Advice from the Experts

Dermatomyositis

Filling in the Gaps in our Knowledge

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Disclosure (previous 12 months)

- Safety Monitoring Committee – Principia Biopharma
- Consultant – Arena Pharma
- Equity Holdings (Personal/Spouse): Celgene; Pfizer; 3M; Johnson and Johnson; Merck; Abbott Laboratories; AbbVie; Procter and Gamble; Pfizer; Amgen
- None of the above relationships are relevant to my presentation
- I will discuss “off-label” uses of some of the currently available agents and will identify which are labeled v. off-labeled uses.

July 2019
Learning objectives:

• Following this talk, the attendee will be able to:
  – More effectively diagnose cutaneous manifestations of dermatomyositis
  – Understand the gaps in our knowledge about evaluation and management of dermatomyositis
  – Recognize areas for future study

• This will be a case-based discussion
Dermatomyositis (DM) is a clinically recognizable condition with prominent skin and muscle manifestations. It is possible for patients to have skin-predominant disease. DM patients may have disease in other organ systems (e.g. joints, lungs, esophagus, heart). DM is part of a group of idiopathic inflammatory myopathies (IIM). DM is associated with cancer, but a paraneoplastic relationship is uncommon. Muscle disease seemingly is more responsive to therapy than skin disease, however skin disease often has a clinically significant impact on the Quality of Life. The ideal therapy for cutaneous disease has yet to be determined.
DM is a Systemic Disease

• Aside from Cutaneous and muscle disease patients with Dermatomyositis may have:
  – Arthritis
  – Esophageal disease – distal v. proximal
  – Pulmonary disease
  – Cardiac disease
Some of the Unresolved Questions/Controversies

1. What is the appropriate classification for patients with dermatomyositis?
2. What is the relationship between UV light and DM?
3. What is the appropriate malignancy evaluation? When should it be repeated?
4. Are serologic tests useful in DM patients?
5. How effective are antimalarial agents for cutaneous dermatomyositis? & What is the risk of a drug reaction in dermatomyositis patients who are treated with hydroxychloroquine?
6. Should patients be serially assessed with PFTs?
7. What is the best therapy for skin disease?
Controversy #1

What is the appropriate classification of dermatomyositis?
Criteria for Diagnosis of Dermatomyositis

• Bohan & Peter suggested 5 criteria in their seminal 1975 articles on diagnosis and classification of dermatomyositis and polymyositis:
  – Progressive, proximal, symmetrical weakness
  – Elevated muscle enzymes
  – Abnormal EMG
  – Abnormal Muscle biopsy
  – Compatible skin disease

• Observational, retrospective, multicenter study.
• Patients identified from the Neuromuscular Diseases Reference Centre of Paris from 2003-2016.
• Inclusion criteria: adult myositis defined according to historical classifications of PM, DM and IBM, and MSA screening.

JAMA Neurol. 2018 Dec 1;75(12):1528-1537
Results

• Cluster 3 (corresponds to DM)
• 20% of patients with IIM
  – 40 years or younger, 100% had skin lesions, primarily DM rash, heliotrope rash, shawl sign, limb edema, skin ulcers, alopecia, calcinosis and/or panniculitis.
  – Severe proximal muscle weakness, mostly affecting deltoids
• Muscle biopsy showed perifascicular atrophy in 56%, and inflammation with perivascular infiltrates
• Anti-Mi2 was most commonly seen MSA (19%)
  – 83% of Mi-2 patients were in this cluster
• Majority of cancers were observed in this cluster (21%)
• Anti-MDA5 (5.8%) and TIF-1-γ (3.8%)
Results

- Cluster 4 (corresponds to anti-synthetase syndrome)
- 22.5% African heritage, 38% 40 years or younger at diagnosis.
- Skin lesion criteria in 80%, 55% with *mechanic hands*.
- Normal or subnormal muscle strength in proximal muscles (deltoids, psoas and quadriceps)
- CK levels highly elevated.
- Biopsy showed perivascular infiltrates in 53%
- 88% had *antisynthetase antibodies* (Jo1 was 100% specific, anti-PL7 and SSA also seen)
- 100% had lung-specific involvement (frequently diffuse interstitial lung disease), and many had arthralgia, arthritis and Raynaud phenomenon.
- Cancers very rare (2.5%)
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<td>22 (55.0)&lt;sup&gt;c&lt;/sup&gt;</td>
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Cluster 1 = IBM, Cluster 2 = IMNM, Cluster 3 = DM, Cluster 4 = anti-synthetase assoc. myositis
2017 EULAR/ACR Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies

• Dermatomyositis (DM): Heliotrope or Gottron’s papules or Gottron’s sign with any 1 pattern of weakness.
• Amyopathic DM: any 1 of the characteristic DM rashes, without weakness
• Polymyositis (PM) (AKA Immune-mediated necrotizing myopathy, IMNM): no characteristic rashes, requires muscle biopsy
• Inclusion body myositis (IBM): No characteristic rashes. One of these 2 are required for diagnosis: Finger flexor weakness and response to treatment: not improved, or Muscle biopsy: rimmed vacuoles
• JDM: Age onset < 18 years, 1 of the characteristic DM rashes
• Juvenile Myositis other than JDM: onset <18yo without 1 of the characteristic DM rashes
Patient meets the EULAR/ACR classification criteria for IIM

Age at onset of first symptom < 18

No

Heliotrope rash or, Gottron's papules or, Gottron's sign

No

Clinical features* or, Muscle biopsy feature**

PM (IMNM)

IBM

Yes

Objective symmetric weakness, usually progressive, of the proximal upper extremities or, Objective symmetric weakness, usually progressive, of the proximal lower extremities or, Neck flexors are relatively weaker than neck extensors or, In the legs proximal muscles are relatively weaker than distal muscles

No

ADM

Yes

DM

Juvenile myositis other than JDM***

Yes

Heliotrope rash or, Gottron's papules or, Gottron's sign

No

Yes

JDM
Controversy #2

What is the relationship between UV light and 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

Controversy #3

What is the appropriate evaluation for malignancy in adults with dermatomyositis, and when should the evaluation be repeated?
52 y/o man was first seen in Jan. 2009

- 2-month history of a minimally pruritic rash on hands and face with slight swelling of the eyelids
- Seen by a prior dermatologist who performed a biopsy which revealed “an interface dermatitis”
- PMH – IDDM, hypertension, sleep apnea, GERD, hypercholesterolemia
- Medications: Simvastatin, pentaprozole, insulin, aspirin, omega-3, amlodipine/benazepril
Physical Examination

• Slight eyelid edema, but no discoloration
• Normal strength
• No joint inflammation
• Skin findings on the dorsal hands characteristic of dermatomyositis
Diagnosis

- “Amyopathic” dermatomyositis (ADM)
- Possibility of a drug-induced cause for the findings was entertained as he had only been on the following therapies for a relatively short time:
  - Simvastatin, amlodipine/benazepril – 8 months
  - Pentaprozole – 3 months
Evaluation

- Muscle-derived enzymes – CK, aldolase
- Serologic evaluation
- Immunofixation electrophoresis
- Malignancy evaluation
  - Physical examination including testicular examination and stool hematest
  - CT scans – chest, abdomen and pelvis
- Pulmonary function studies
- Barium swallow
Results

• All examinations and testing were normal except for a 1.2 cm lesion in the upper pole of the left kidney suggestive of a renal cell carcinoma

• Referred for urologic evaluation and a Grade III renal cell carcinoma was removed on 2-11-09
Course

- No changes noted with drug cessation
- No changes in rash following cancer surgery
- Progressively noted fatigue, but strength has been clinically normal and enzymes consistently normal
- Little response to methotrexate 25 mg/w for 3 months, placed on mycophenolate mofetil
- Eventually remitted at 1 year and now has been off all therapy for about 7 years.
REVIEW

Dermatomyositis and Malignancy

A Review of the Literature

BARBARA E. BARNES, M.D., Bryn Mawr, Pennsylvania

Annals of Internal Medicine 84:68-76, 1976
The Relationship of Dermatomyositis and Polymyositis to Internal Malignancy

Jeffrey P. Callen, MD; James F. Hyla, MD; Giles G. Bole, Jr, MD; Donald R. Kay, MD

The association of malignancy with dermatomyositis and polymyositis has been questioned. During the last 20 years (1956 to 1975), we have studied 58 cases of myositis that met predefined diagnostic criteria. These cases were analyzed for the frequency of malignancy, prognosis, and the value of a diagnostic test series for malignancy. A significantly greater frequency of malignancy was found with dermatomyositis than with polymyositis. The prognosis of dermatomyositis and polymyositis appears to be altered in the presence of malignancy. In the absence of malignancy, the prognosis is similar in the two forms of myositis. Lastly, the value of a screening laboratory and roentgenographic investigation for the presence of occult malignancy beyond a thorough history, physical examination, and the use of basic laboratory tests such as complete blood count, stool guaiac test, urinalysis, multiphasic analysis, and chest roentgenogram was not documented by this study.

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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<td>4.39</td>
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**Rate ratio and 95% CI**

![Image showing decreased and increased risk](image-url)
Malignancy-associated dermatomyositis: Retrospective case–control study from a single tertiary care center

Length of time between the diagnosis of DM and the diagnosis of malignancy

- Malignancy Before DM
- Time of DM Diagnosis
- Malignancy After DM

Number of Patients

2-3y: 4 | 1-2y: 5 | <1y: 13 | <1y: 16 | 1-2y: 5 | 2-3y: 7

Length of time between the two diagnoses in years

ADULT DERMATOMYOSITIS & MALIGNANCY

- Preceding malignancy
- Concurrent Malignancy
- Subsequent malignancy
- No cancer
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
CONVENTIONAL CANCER SCREENING VERSUS PET/CT IN DERMATOMYOSITIS/POLYMYOSITIS

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.
18F-FDG PET/CT versus conventional investigations for cancer screening in autoimmune myopathy in the era of novel myopathy classifications.

Maliha PG¹, Hudson M², Abikzer G³, Sgierman J⁴, Probst S³.

Abstract

BACKGROUND: To compare the performance of fluorine-18-fluorodeoxyglucose (F-FDG) PET/computed tomography (CT) and conventional tests for cancer screening in autoimmune inflammatory myopathy (AIM) patients.

PATIENTS AND METHODS: We carried out a retrospective cohort study of AIM patients from one academic center in Montreal, Canada, classified using myositis-specific antibodies, who underwent F-FDG PET/CT between April 2005 and February 2018 and were followed up on average 3.5±2.4 years. Patients were excluded if follow-up was insufficient, AIM diagnosis was indeterminate, and/or malignancy was diagnosed before an F-FDG PET/CT scan. Demographic/clinical data, F-FDG PET/CT results, and available conventional screening tests results were retrieved from electronic and paper medical records.

RESULTS: 100 F-FDG PET/CT studies in 63 unique patients (31/63 dermatomyositis (DM), 25/63 overlap myositis, 1/63 inclusion body myositis, 1/63 polymyositis, 1/63 orbital myositis and 4/63 unspecified myositis) were evaluated. Three patients, all classified as DM, were diagnosed with cancer during follow-up with conventional cancer screening tests: breast cancer detected by mammography; squamous cell carcinoma of the skin detected by physical examination; and multiple myeloma detected by blood work. F-FDG PET/CT did not detect any malignancy and led to more additional biopsies than conventional screening (8 vs. 5).

CONCLUSION: F-FDG PET/CT does not appear to be useful in cancer screening for AIM patients compared with conventional screening and carries potential harms associated with follow-up investigations. The risk of cancer in AIM differs by myositis-specific antibodies-defined subsets and cancer screening is likely to be indicated only in high-risk patients, particularly DM. These results, replicated in larger, multicentered studies, may carry significant consequences for optimal management of AIM and health resource utilization.

PMID: 30664602 DOI: 10.1097/MNN.0000000000000981
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 for Malignancy

- 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
- Repeat annually for 3 years, then perform cancer screening indicated for any person based upon their age, sex, ethnicity, etc.
- Evaluate any new symptom
- Remaining issue is how to handle a patient in remission for several years, but who develops a relapse – Should a malignancy evaluation be performed?
Controversy #4

Is testing for myositis specific or associated antibodies clinically useful?
52-year-old woman

- Dermatomyositis diagnosed at age 33 with skin and muscle disease
- Malignancy evaluation during the first three years following diagnosis was repeatedly negative
- Treatments have varied, but included combinations of methotrexate, mycophenolate, hydroxychloroquine, IVIG and most recently tofacitinib
- Annual physical examination and “routine” malignancy screening has been normal or negative
2017 MSA testing became available

- ANA – negative
- TIF-1γ – positive
- Mi-2 – negative
- NXP – negative
- MDA5 - negative
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]).

Use of Anti-transcriptional Intermediary Factor-1 Gamma Autoantibody in Identifying Adult Dermatomyositis Patients with Cancer: A Systematic Review and Meta-analysis

Anti-transcriptional intermediary factor-1γ (TIF-1γ) autoantibody may be associated with cancer in adult patients with dermatomyositis. The aim of this study was to evaluate the risk of cancer in the presence of anti-TIF-1γ autoantibody in adult dermatomyositis. A comprehensive database search of EMBASE, MEDLINE and the Cochrane Library up to May 2018 was performed using the main key words “dermatomyositis”, “myositis”, “inflammatory myopathies” and “anti-TIF-1”. Eighteen studies, with a total of 1,962 dermatomyositides, were included in the meta-analysis. The pooled prevalence of cancer-associated dermatomyositis in patients with anti-TIF-1γ autoantibody was 0.41 (95% confidence interval (CI) 0.36–0.45). In the presence of anti-TIF-1γ autoantibody, the overall diagnostic odds ratio of cancer was 9.37 (95% CI 5.37–16.34) with low heterogeneity (Cochran’s Q: 14.88 (df = 17, p = 0.604); I² = 0%). The results of this systematic review confirm that detection of anti-TIF-1γ autoantibody is a valuable tool to identify a subset of adult dermatomyositis patients with higher risk of cancer.
Use of MSAs in practice

- There is a question about the validity and reproducibility of testing in commercial laboratories.
- The testing in research laboratories is not widely available and the results are often delayed by weeks or months.
- The associations between antibody results and risks of malignancy or pulmonary disease are statistically valid, but there are patients with disease in whom antibodies are not present and those without associated disease in whom the testing was positive.
- Bottom line: Clinical assessment for pulmonary disease and malignancy should not be replaced.
Controversy #5

How effective are antimalarial agents for cutaneous dermatomyositis? & What is the risk of a drug reaction in dermatomyositis patients who are treated with hydroxychloroquine?
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
Antimalarial Therapy of DM

• Dosage
  – Hydroxychloroquine – 200 to 400 mg/d
  – Chloroquine – 250 to 500 mg/d
  – Quinacrine – 100 mg bid

• Onset of effect – 4 to 8 weeks

• Monitor – usual methods

• If a drug eruption occurs, can another antimalarial agent be used?
Antimalarials – Is there an increased risk of cutaneous drug reactions in patients with dermatomyositis?

- Case-control study of 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
  - 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.

Pelle MT, Callen JP: Adverse cutaneous reactions to hydroxychloroquine are more common in patients with dermatomyositis than in patients with cutaneous lupus erythematosus. Arch Dermatol 2002;138:1231-3
• Study at Harvard, NYU, Loyola & Stanford
• 115 pts (93 amyopathic, 22 hypomyopathic)
• 88 pts (76.5%) used antimalarial therapy
• Only 10 pts. (11.4%) were deemed responsive to therapy
• 27 pts (30.7%) developed a morbilliform eruption
• Differences in therapies utilized depended upon whether the patient was followed in Dermatology or Rheumatology Clinics

Published Online: January 23, 2019. doi:10.1001/jamadermatol.2018.5215
## Table 1. Characteristics of Study Population

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<sup>a</sup>Statistically significant.
Controversy #6

How should patients be assessed for pulmonary disease? & Should patients be serially assessed?
Pulmonary Disease associated with Dermatomyositis

- Interstitial pneumonitis
  - Polymyositis patients associated with anti-synthetase antibodies (particularly Jo-1)
  - Amyopathic dermatomyositis with MDA5 antibodies
- Aspiration – correlates with esophageal disease
- Hypoventilation due to weakness suggests grave prognosis
- Drug-induced hypersensitivity (e.g. methotrexate)
- Infectious complication in the immunosuppressed patient
Interstitial Lung Disease in DM

- This retrospective cohort study involved 91 patients with dermatomyositis, 71 of whom had pulmonary function tests, including carbon monoxide diffusion (DLCO) tests or high-resolution computed tomography (CT) scans.
- Of these 71 patients, 35 had skin-predominant disease, and 36 had classic DM; ILD prevalence did not differ by disease type.
- Sixteen patients had CT-defined ILD, and 18 others had abnormal DLCOs.
- Jo-1 antibodies (associated with inflammatory myopathies) were absent in all 50 patients tested.

Morganroth PA et al. Arch Dermatol 2010 Jul; 146:729
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)
  - **OBTAINT HRCT**

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

  - **NEGATIVE FOR ILD**
    - **OBTAINT ECHOCARDIOGRAM TO R/O PULMONARY HTN AND CBC TO R/O ANEMIA AND REFER TO PULMONARY**

  - **POSITIVE FOR ILD**
    - **REFER TO PULMONARY**
Controversy #7

What is the optimal therapy for cutaneous lesions of dermatomyositis?
Therapy of Cutaneous DM

- Sun-protective measures – behavior, sunscreens, protective clothing
  - Assess Vitamin D levels and/or supplement
- Topical emollients, corticosteroids, calcineurin inhibitors
- Antimalarial agents
- Methotrexate
- Mycophenolate mofetil
- IVIG
- Other agents – dapsone, thalidomide, leflunomide, sirolimus, chlorambucil, etanercept, infliximab, rituximab, apremilast, ACTH gel, tofacitinib, lenabasum (JBT-101) an oral cannabinoid (20 mg) that is anti-itch (anti-IL-31)*

* FDA recently granted orphan drug approval
Conclusions

• Dermatomyositis is a multisystem disorder with primary manifestations in the skin and muscles
• Adults with DM should be assessed for malignancy
• Assess for other potential systemic manifestations, particularly pulmonary disease
• Successful management is possible