MYalgias,
MYopathies,
MYositis,
Oh MY!

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• **Diclosures**: Research support from Pfizer, Abbvie, Astra-Zeneca, Bristol-Meyers Squibb, Novartis, Genentech, Aurinia Pharmaceuticals, Pfizer

• The following talk includes “off-label” discussion of mycophenolate mofetil, azathioprine, methotrexate, leflunomide, cyclophosphamide, cyclosporine, tacrolimus, rituximab.
Learning Objectives

• Understand how to assess patients with elevated Creatine Kinase (CK), muscle pain, and/or muscle weakness
• Distinguish among the different types of myositis and myopathies
• Manage patients with immune mediated muscle complaints
Case 1

33 y.o. black male was noted on labs to have CK 536 IU/L. Exam was unremarkable. He cited occasional fatigue.

Asymptomatic hyper-CK-emia can be found with all of the following EXCEPT?

a. Normal physiology: male sex, race
b. Hypothyroidism
c. Hypogonadism
d. Muscle cramps
e. Ethanol use
Physiologic etiology of isolated CK elevation:

- Exercise raises CK (may increase 30 X ULN after vigorous exercise or heavy manual labor within 24 hours of activity and will slowly decline after 7 days)
  - Norwegian study noted 70% of CK normalize after 3 days of rest. Neuromuscul Disord. 2011 Jul; 21(7):494-500.
- Pregnancy
Asymptomatic hyperCKemia

- Most labs use central 95% of observation in white people as a reference range for serum CK with bell shaped curve 0-200 IU/L (abnormal CK will be seen in 13% of the white Europeans, 23% of South Asians, and 49% of the black people with this threshold)
- 97.5% normal threshold recc by European Academy of Neurology (1.5 X ULN):
  - White women—325 IU/L
  - White men—504 IU/L
  - Black women—621 IU/L
  - Black men—1,200 IU/L

Remember the other markers of muscle enzymes: aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and aldolase.
Elevated CK

Non-physiologic causes of elevated CK:

• Endocrine (↓ thyroid, ↑ PTH, NOT hypogonadism)
• Autoimmune
• Cardiac & renal disease
• Viral illness
• Metabolic & congenital
• Trauma
• Malignancy
• Macro CK
• Electrolytes (↓ Na/K/Phos)

• Medications:
  – statins/fibrates
  – antiretrovirals
  – beta-blockers w/ISA
  – anti-psychotics
  – angiotensin receptor blockers
  – hydroxychloroquine
  – colchicine
  – isotretinoin

Recreational drugs: cocaine, heroin, EtOH

Asymptomatic hyperCKemia

Algorithm for evaluating asymptomatic hyperCKemia

Is CK > 1.5 X ULN?
- Nonblack female >325 U/L
- Nonblack male >504 U/L
- Black female >621 U/L
- Black male >1201 U/L

No → Observe

Yes →

1. Repeat CK with fractionate for CK-MM.
2. Patient should rest for 7 days

CK still abnormal?

No →

Yes → Exclude non-neuromuscular causes (thyroid, medications, metabolic, etc)

EMG/NCS, muscle biopsy
Asymptomatic hyperCKemia

- **EMG/NCS:** pro’s- distinguish myopathic from neuropathic changes, modest negative predictive value
  con’s – poor specificity; nonspecific changes in 50% pts
- **Yield of muscle biopsy:** 50-60% nonspecific changes; 20-25% had myopathic diagnosis; special histochemical stains needed\(^1,2\)
- **European Federation of Neurological Societies guidelines\(^3\) recommend muscle biopsy if:**
  - EMG is abnormal: myopathic findings
  - CK > 3 X upper limit of normal
  - Age < 25
  - Exercise intolerance

**If workup is nondiagnostic, longterm followup of asymptomatic hyperCKemia is NOT needed**

66 y.o. diabetic white female on atorvastatin and metformin presented:
- severe muscle pain in her shoulders and hips
- morning stiffness 2 hours
- poor sleep
- Exam: mild limitation to B shoulder flexion and abduction and tenderness to B trochanteric bursae. No synovitis
- Labs: WBC 6.8, Hgb 10.1, Plt 448, Cr 0.9, CK 270 U/L aldolase 3.4 U/L(nl 1.0-7.5). ESR 55 mm/hr, CRP 2.1 mg/dL.

**What is the most appropriate next step?**

a. **Stop atorvastatin, repeat CK in 2-4 weeks**

b. **Obtain EMG/NCS and muscle biopsy**

c. **Order shoulder MRI to evaluate rotator cuff disease**

d. **Start prednisone 12.5-25 mg/day for polymyalgia rheumatica**

e. **Start pregabalin and physical therapy for fibromyalgia**
Myalgias

- CDC noted chronic pain can occur in 11-44% of US adults
- Differential diagnoses of chronic pain:
  - Soft tissue pain syndrome (fibromyalgia, depression, somatoform d/o)
  - Drug toxicity (statins, AZT, ethanol, cyclosporin, clofibrate, penicillamine)
  - Chronic infections (HBV, HCV, HIV)
  - Endocrine diseases (thyroid/parathyroid disease, diabetes, acromegaly, adrenal disease)
  - Malignancy
  - Multiple Sclerosis
  - Immune mediated inflammatory disease (polymyositis, dermatomyositis, polymyalgia rheumatica, rheumatoid arthritis, systemic lupus erythematosus, vasculitis)
  - Osteoarthritis
  - Vitamin deficiencies (vit D, B12)

MMWR. September 14, 2018 / 67(36);1001–1006
The Internist’s Top 3 DDx for Myalgias:
(aside from the flu/other viruses)
1. Fibromyalgia
2. Statin-related myalgias/myopathy
3. Polymyalgia rheumatica
Fibromyalgia Syndrome

• Fibromyalgia syndrome, NOT Fibromyalgia disease
• chronic pain, fatigue, and functional symptoms
• Etiopathogenesis: genetic? environmental? neuromodulation?
• Role of:
  1. Poor sleep --> pain and cognitive disturbances
  2. Social stress --> lowers threshold of pain sensitivity; in younger patients eval for trauma/abuse
  3. Lack of Exercise
Fibromyalgia Syndrome

ACR 2016 Revised Diagnostic Criteria for FM

- Widespread pain index (WPI*) and symptom severity score (SSS**): WPI ≥ 7 and SSS ≥ 5 OR WPI 4-6 and SSS ≥ 9
- Generalized pain: pain in 4/5 regions
- Symptoms present ≥ 3 months
- FM diagnosis can be made irrespective of other diagnoses (you do not need to rule out all other conditions that could explain the symptoms, if criteria 1-3 are all met).

*jaw, shoulder girdles, R and L upper/lower arm, hips, R and L upper/lower leg, chest, abdomen, neck, upper and lower back (score 0-19)

**cognitive and somatic symptoms (score 0-3): fatigue, unrefreshed sleep, IBS, frequent urination, numbness, headaches, abd pain/cramping, depression

Semin Arthritis Rheum. 2016 Dec;46(3):319-329
<table>
<thead>
<tr>
<th>Nonpharmacologic</th>
<th>Pharmacologic</th>
</tr>
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<tbody>
<tr>
<td>• patient education</td>
<td>• low dose tricyclics</td>
</tr>
<tr>
<td>• aerobic exercise</td>
<td>• pregabalin*, gabapentin</td>
</tr>
<tr>
<td>• cognitive behavioral therapy</td>
<td>• duloxetine*</td>
</tr>
<tr>
<td>• acupuncture</td>
<td>• milnacipran*</td>
</tr>
<tr>
<td>• transcranial direct current stimulation</td>
<td>• SSRIs</td>
</tr>
<tr>
<td>• music Clin Rheumatol. 2016 May;35(5):1317-21.</td>
<td>• muscle relaxants</td>
</tr>
<tr>
<td></td>
<td>• dopaminergic agonists (pramipexole)</td>
</tr>
<tr>
<td></td>
<td>• tramadol</td>
</tr>
<tr>
<td></td>
<td>• cannabinoids (?)</td>
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</tbody>
</table>

*FDA approved therapies for FM
• Statin associated muscle symptoms (SAM) is a major reason for statin nonadherence: elevated CK, myalgias, myopathy, myositis, rhabdomyolysis

• How do statins cause SAM? decrease mitochondrial function, attenuate energy production and alter muscle protein degradation

• In RCTs statin associated adverse muscle related events similar to placebo and statin group (5-10%), higher rates in observational studies (up to 29%)
Statin Myopathy/Statin Myositis

- STOMP study (Effects of Statins on Muscle Performance) only RDBPCT examined statins’ role on SkM symptoms and performance.
  - 420 statin naive given atorvastatin 80 mg/d vs PCB X 6 months
  - 9.4% statins vs. 4.6% PCB had myalgias
  - no difference b/t muscle strength or performance
  - Over 90% of patients who have stopped treatment because of an adverse event can tolerate a statin if re-challenged

_Circulation_. 2013 Jan 1; 127(1):96-103.
Statin Myopathy/Statin Myositis

Risk factors for statin myopathy:

- advance age (caution in those > 75 y.o)
- Untreated/undertreated hypothyroidism
- Drug interaction w/P450 pathway (fibrates, amiodarone, macrolide antibiotics, azoles, protease inhibitors and warfarin)

Note: Fluvastatin and rosuvastatin are not CYP3A4 substrates and are less prone to drug interactions. *Clin Pharmacol Ther. 2006 Dec; 80(6):565-81.*

Statin Myopathy/Statin Myositis

- Highest offending agents are most lipophilic: simvastatin, atorvastatin, lovastatin
- Least likely to cause SAM: pravastatin, rosuvastatin, and fluvastatin
- Symptoms/CK typically improve 1-6 months after stopping statins
American College of Cardiology Statin Intolerance App:

Statin Induced Autoimmune Myopathy

- If symptoms and high CK (>10 X ULN) persist despite stopping statins, consider Statin Induced Autoimmune Myopathy in the presence of +HMG-Co-A R (HMGCR) Ab

- In vitro, statins increase HMGCR expression in muscle cells, an autoantigen in Immune Mediated Necrotizing Myopathy (IMNM)

- Regenerating muscle cells express high levels of HMGCR, which may sustain the immune response even after statins are discontinued.

- Interestingly, 33% of anti-HMGCR Ab positive symptomatic patients were NOT previously exposed to statins (e.g, children and young adults have worse prognosis). Risk factors: HLA-DRB1*11:01 and 07:01 alleles

Statin Induced Autoimmune Myopathy

Clinical Features:
1. Progressive **proximal** weakness w/skeletal muscle involvement: posterior/medial thigh and gluteals
2. Dysphagia 16-30%
3. CK 1000-20,000 IU/L
4. EMG: myopathic w/spontaneous activity in forms of fibrillations and sharp waves
5. MRI Imaging: T1 hyperintensity esp. posterior thigh; STIR signal increased and may be asymmetric
6. Muscle bx: myofiber degen. & necrosis w/variable density of regenerating fibers

Polymyalgia Rheumatica (PMR)

- **Classic board question**: Patient > 50 y.o. (typically Caucasian) w/girdle muscle pain, elevated inflammatory markers, dramatic response to low dose glucocorticoids (GCs)

- **Barriers to diagnosis**:
  - Many other conditions respond to low dose GC’s: RA, OA, polymyositis
  - 5% PMR patients have normal ESR/CRP
  - 1/3 PMR patients do not have complete responses to GCs even after 3-4 wks

Arthritis Rheum. 2007; 57: 803-09
2012 ACR/EULAR Provisional Classification Criteria for PMR

Required criteria: age 50 years or older, bilateral shoulder aching and abnormal C-reactive protein and/or erythrocyte sedimentation rate

Clinical criteria for scoring algorithm:*  
1. Morning stiffness lasting more than 45 min  
2. Hip pain or restricted range of motion  
3. Absence of rheumatoid factor and antibody to cyclic citrullinated peptide  
4. Absence of other joint involvement  

Ultrasound criteria for scoring algorithm:*  
5a. At least one shoulder with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis; and at least one hip with synovitis or trochanteric bursitis  
5b. Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis

*With only clinical criteria, a score of ≥4 had a sensitivity of 68% and specificity of 78% for discriminating polymyalgia rheumatica from comparison patients. With a combination of clinical criteria and ultrasound criteria, a score of ≥5 had a sensitivity of 66% and specificity of 81% for discriminating patients with the disorder from comparison patients.
Polymyalgia Rheumatica (PMR)

2015 ACR/EULAR recommendations for the management of PMR

Start oral prednisone equivalent 12.5–25mg/day:

- Consider MTX if at high risk for side effects/relapse and/or prolonged therapy

Clinical improvement at 2–4 wk?

- yes
  - Gradual tapering of glucocorticoids
  - Remission
  - Taper prednisone until discontinuation

- no
  - Confirmation of PMR
  - yes
  - Increase steroid dose

- no
  - Re-assess
  - Diagnosis in question

Case 3

70 y.o. male with diabetes and HTN with:
- weakness for >6 months.
- difficulties with getting up from a seated position
- difficulties with combing his hair
- difficulties writing his name using a pen

Exam noted 4+/5 muscle strength L<<R side; he cannot maintain a grip against resistance.
Labs: CBC nl, Cr 1.15, AST 45, Alt 39, CPK 850, ESR 25.

What is the likely diagnosis?

a. Polymyositis
b. Polymyalgia rheumatica
c. Diabetic myonecrosis
d. Inclusion body myositis
e. Cerebrovascular accident (CVA)
## Idiopathic Inflammatory Myopathies

Characterized by muscle weakness and immune mediated inflammation

<table>
<thead>
<tr>
<th>IIM Subtypes</th>
</tr>
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<tbody>
<tr>
<td>Juvenile dermatomyositis</td>
</tr>
<tr>
<td>Dermatomyositis</td>
</tr>
<tr>
<td>Amyopathic dermatomyositis</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
</tr>
<tr>
<td>Polymyositis</td>
</tr>
<tr>
<td>Immune-mediated necrotizing myopathy</td>
</tr>
</tbody>
</table>

Idiopathic Inflammatory Myopathies:

**Immunopathogenesis**

- Infiltrates - T cells & monocytes
- Muscle fibers express class I & II MHC Ags
- T cells are cytotoxic to muscle fibers
- T cells are proinflammatory, apoptosis resistant cytotoxic CD4\(^+\) and CD8\(^+\) CD28\(^{\text{null}}\)
- t-RNA antibodies: FOUND IN <50% OF PTS
- Infectious etiology? Viral implicated
- HLA-B8/DR3 in childhood DM
- DR3 and DRW52 with t-RNA synthetase Ab
<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;18 and &lt;40 yrs</td>
<td>1.3</td>
</tr>
<tr>
<td>Age &gt; 40 yrs</td>
<td>2.1</td>
</tr>
<tr>
<td>Objective symm progressive muscle weakness:</td>
<td></td>
</tr>
<tr>
<td>prox UE, prox LE,</td>
<td>0.7-0.8</td>
</tr>
<tr>
<td>neck flexor &lt;&lt; extensors</td>
<td>1.9</td>
</tr>
<tr>
<td>in legs, prox muscles &lt;&lt; distal muscles</td>
<td>0.9</td>
</tr>
<tr>
<td>Skin manifestations</td>
<td></td>
</tr>
<tr>
<td>Heliotrope rash</td>
<td>3.1</td>
</tr>
<tr>
<td>Gottron’s papules/sign</td>
<td>2.1-3.3</td>
</tr>
<tr>
<td>Dysphagia or esophageal dysmotility</td>
<td>0.7</td>
</tr>
<tr>
<td>Lab abnormalities:</td>
<td></td>
</tr>
<tr>
<td>Jo-1 antibody</td>
<td>3.9</td>
</tr>
<tr>
<td>Elevated CK, LDH, AST/ALT</td>
<td>1.3</td>
</tr>
<tr>
<td>Muscle biopsy features:</td>
<td></td>
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<tr>
<td>Endomysial infiltrates not invading myofibers</td>
<td>1.7</td>
</tr>
<tr>
<td>perimysial/perivascular infiltration</td>
<td>1.2</td>
</tr>
<tr>
<td>perifascicular atrophy</td>
<td>1.9</td>
</tr>
<tr>
<td>rimmed vacuoles</td>
<td>3.1</td>
</tr>
</tbody>
</table>

2017 EULAR/ACR classification criteria for IIM

**definite IIM:** score
- ≥7.5 w/o biopsy,
- ≥8.7 w/ biopsy

**probable IIM:** score
- ≥5.5 w/o biopsy,
- ≥6.7 w/ biopsy
Idiopathic Inflammatory Myopathies (IIM)

Patients meet criteria for IIM

No

Age <18

Yes

Heliotrope rash
Gottren’s papules/sign

No

Clinical features or Muscle biopsy feature

No

PM IMNM

No

Yes

IBM

Heliotrope rash
Gottren’s papules/sign

Yes

Objective symmetrical weakness proximal UE/LE or neck flexors << extensors

No

No

PM IMNM

IBM

CADM

DM

Juvenile myositis other than JDM

Yes

JDM

2017 EULAR/ACR Algorithm to identify subgroup of IIM

Polymyositis

- Begins insidiously (3–6 months)
- **Sx:** proximal muscle weakness (shoulder, pelvic girdle/thigh, and neck flexors): Minimal pain, if any
- Facial muscles, distal muscles, and sensation are spared
- Dysphagia, Dysphonia, Dyspnea
- Raynaud’s phenomenon
- Cardiac: SVTs, cardiomyopathy, CHF
- 65% elevated CPK, aldolase, 50% ANA (+)
- 90% +EMG: low amplitude, short duration, and polyphasic potential; spontaneous fibrillations; and early recruitment.
- 85% + muscle biopsy

Polymyositis

Muscle biopsy

- **endomysial** mononuclear inflammatory infiltrate
- muscle fibers are of variable size
- muscle fiber necrosis
- T lymphocyte (esp CD8+) predominence
Dermatomyositis

Dermatomyositis has same Sx’s as PM plus rash:

• Heliotrope rash
• Gottron sign/papules
• Shawl sign — erythema of shoulders and neck
• Holster (lateral thighs)
• Calcinosis with long standing Dz
• Periorbital edema
• Periungual erythema with dilated nailfold capillaries and dropout
Dermatomyositis

Muscle biopsy

- Interface dermatitis
- Mucin deposition in the dermis
- Vacuolar changes of the columnar epithelium
- **Perivascular and perimysial infiltration** of CD4+ T and B cells, macrophages, DCs
- Walls not necrotic
- Role of microvessels in disease
Immune Mediated Necrotizing Myopathy

- Rare (9-14 per 100,000)
- High CK (median value 5000)
- Severe proximal muscle weakness
- Biopsy: necrotic muscle fibers w/minimal lymphocytic infiltrates (macrophagocytosis)
- Assoc w/ myositis specific Abs:
  - Anti-HMGCR Abs (+/- statins hx)
  - Anti- PL-12 Abs
  - Anti- PL-17 Abs
  - Signal Recognition Particle Ab

Inclusion Body Myositis (IBM)

- Age > 50, may be hereditary
- Slow onset, progressive asymmetric weakness
- Painless, distal and proximal asymmetric weakness; facial muscles can be involved
- Dysphagia can lead to aspiration pneumonia
- Normal or mildly elevated CPK (usually <2,000 IU/ml)
- Poor response to corticosteroids, immunomodulators, and IVIG

Greenberg. *Curr Opin Rheumatol.* 2011 Nov;23(6):574-8
Inclusion Body Myositis (IBM)

- **Dx:** light microscopy normal. Rimmed vacuoles and tubulofilamentous inclusion bodies on EM
- **Role for amyloid? NT5C1A ab?**
- **New Rx:** Alemtuzumab (Campath)

**EM:** vacuoles with tubofilamentous inclusions

**Congo red stain:** amyloid deposits

Greenberg, *Curr Opin Rheumatol.* 2011 Nov;23(6):574-8
## IIM: PM, DM, IBM

<table>
<thead>
<tr>
<th></th>
<th>DM</th>
<th>PM</th>
<th>IBM</th>
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<tr>
<td><strong>Onset</strong></td>
<td>Early</td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td><strong>M/F</strong></td>
<td>F&gt;M</td>
<td>F&gt;M</td>
<td>M&gt;F</td>
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<tr>
<td><strong>Weakness</strong></td>
<td>proximal</td>
<td>proximal</td>
<td>distal+proximal</td>
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<tr>
<td><strong>Typical pathology</strong></td>
<td>Perifascicular, perivascular infiltrates</td>
<td>Endomysial infiltrates (Invasion of individual fibers)</td>
<td>Rimmed vacuoles, tubofilamentous inclusions</td>
</tr>
<tr>
<td><strong>Steroid Sensitivity</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Case 4

55 y.o. female with hyperlipidemia and HTN on of lovastatin and hydralazine:

- 2 months fatigue, weakness, and a pruritic rash (photo)
- 12 lbs unintentional weight loss X 2 months

Exam: Difficulties getting up from a seated position to move to the exam table. Enlarged L axillary lymph node and a mass on her L breast.

Labs: WBC 11.5, Hgb 10.8, plt 458, ESR 40, CPK 1750, aldolase 10.1, ANA 1:40 speckled pattern
Case 4

What is the most likely diagnosis?

1. Statin induced myopathy
2. Systemic Lupus Erythematosus with myositis
3. Drug induced lupus
4. Dermatomyositis presenting as a paraneoplastic syndrome
5. Polymyositis
Cancer Associated Myositis (CAM)

- Reports range from 10-25%
- Likelihood of developing cancer is 6X with dermatomyositis, 2X with polymyositis (strongly associated with lymphoma)
- Greatest risk in 1st year: paraneoplastic process
- 60% the myositis appears 1st, 30% neoplasm 1st, and 10% contemporaneously
- Type of cancer reflects characteristics of age, origin, gender
  - Western civilization: breast, lung and colorectal CA
  - Asia: nasopharyngeal CA

## Cancer Associated Myositis (CAM)

Factors Predicting Malignancy in Patients with Polymyositis and Dermatomyositis

<table>
<thead>
<tr>
<th>Variables</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td>age &gt; 45</td>
<td>5.27 (1.92-14.49)</td>
</tr>
<tr>
<td>male sex</td>
<td>1.78 (1.40-2.27)</td>
</tr>
<tr>
<td>cutaneous necrosis</td>
<td>3.36 (2.04-5.52)</td>
</tr>
<tr>
<td>cutaneous vasculitis</td>
<td>6.16 (1.85-20.57)</td>
</tr>
<tr>
<td>dysphagia</td>
<td>2.0 (1.27-3.12)</td>
</tr>
<tr>
<td>onset of Sxs &lt; 4 months</td>
<td>2.22 (1.03-4.82)</td>
</tr>
<tr>
<td>elevated CK</td>
<td>2.42 (1.16-5.04)</td>
</tr>
<tr>
<td>ESR &gt;40 mm/h</td>
<td>2.22 (1.04-4.75)</td>
</tr>
<tr>
<td>anti-p155 Ab</td>
<td>5.57 (2.91-10.65)</td>
</tr>
</tbody>
</table>

Based on systematic review and meta-analysis of 28 cohort studies in patients with PM/DM and malignancy

Protective factors: ENA antibodies, ILD, Raynaud’s

Cancer Associated Myositis (CAM)

- Tends to have rapid, severe onset, worse prognosis
- Age appropriate CA screening vs blind screening
  - 2 large US dermatology cohort 400 patients:
    - 48 pts (12%) with 53 cancers: 40% within 1 year of Sx’s
    - 27 (6.8%) had undiagnosed malignancy at time of dermatomyositis diagnosis
    - 59% of cancers found on CT scans in asymptomatic patients
  - consider evaluation beyond "age appropriate cancer screening“ in patients with high risk factors (e.g, rapid onset, age > 45, male): CT/PET scan
- Antibodies assc with CAM:
  - Anti-MDA-5
  - NXP-2 Abs
  - Anti-p155 antibodies target TIF1 proteins

Cancer-associated dermatomyositis (DM) and anti-p155 autoantibodies

- **Background:** Anti-p155 autoantibody is directed against transcription intermediary factor 1 gamma (TIF-1γ). TIF-1 proteins have positive and negative regulatory roles in carcinogenesis.
- **Meta-analysis of 6 studies (312 pts) assoc w/anti-p155 Ab w/ CA-DM**

![Graph showing sensitivity, specificity, positive predictive value, and negative predictive value.]

A DM pt anti-p155 positive has a OR= 27X higher risk cancer-associated myositis

Other Immune Mediated Myositis
Clinically Amyopathic Dermatomyositis

- AKA Dermatomyositis sine myositis, Clinically amyopathic dermatomyositis (CADM)
- ILD associated w/ poor outcomes in PM/DM
  - CADM-ILD rapidly progressive ILD & 6-mo survival 40.8%
  - DM-ILD also a progressive pattern & 5-year survival 54%
  - PM-ILD more chronic: 5 & 10-yr survival 72.4% and 60.3%
- 291 adult-onset CADM, 73%F, 13% developed weakness 15mos-6yrs after. < 15% develop ILD or neoplasis.
  - 63% ANA+ (3.5% +anti-synthetase Abs)
- Anti-CADM 140 Abs: Raynauds, ILD, severe skin dz

Clin Rheum 2007;26:1647
J Am Acad Dermatol 2006; 54: 597
Anti-Synthetase Syndrome

anti-tRNA synthetase antibody
+
Myositis + ILD + Arthritis + Raynauds + Mechanic’s hands

### Anti-Synthetase Antibodies

<table>
<thead>
<tr>
<th>Anti-ARS antibodies</th>
<th>Auto-antigen</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Jo1*</td>
<td>histidyl</td>
<td>Most common</td>
</tr>
<tr>
<td>Anti-PL7*</td>
<td>theronyl</td>
<td>Severe ILD</td>
</tr>
<tr>
<td>Anti-PL12*</td>
<td>alanyl</td>
<td>Severe ILD</td>
</tr>
<tr>
<td>Anti-OJ*</td>
<td>isoleucyl</td>
<td></td>
</tr>
<tr>
<td>Anti-EJ*</td>
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<td>Anti-JS</td>
<td>glutaminyl</td>
<td></td>
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<tr>
<td>Anti-YRS</td>
<td>tyrosyl</td>
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ILI = Interstitial lung disease

Pearl: In patients with idiopathic ILD/ARDS, consider anti-synthetase syndrome

DM, PM, amyopathic DM/isolated ILD, isolated ILD

Idiopathic Inflammatory Myositis Treatment

• Early Dx, physical therapy, respiratory support
• Corticosteroids: prednisone 1-2 mg/kg/day
• 80% respond within 12 weeks
• Steroid sparing agents (off label):
  – Methotrexate
  – Azathioprine
  – Leflunomide
  – Methotrexate - Leflunomide
  – Azathioprine - Mycophenolate mofetil
  – Leflunomide - Tacrolimus, Cyclosporine
• IVIG (2 g/kg/day X 3-5 days)
• No response to apheresis, TNF inhibitors
• ?? Rituximab
INFLAMMATORY MYOSITIS
Future Therapies

- α Interferon Abs
- Anti-lymphotoxin mAbs (TNFβ)
- Anti-Cytokine (IL6? IL-1?)
- Abatacept (CTLA-4 Ig)
- Tofacitinib (JAK inhibitor)
- Autologous Stem Cell Transplantation

Prognosis

- Adults: 10-year survival rates for PM 55% (47-62%) and DM 53% (41-64%).
- Poor prognosis in pts. with delayed Dx, low CK, early lung or cardiac findings, malignancy
- Kids: 50% remission, 35% chronic active dz
- Relapses & functional disability are common
- Death: due to malignancy, sepsis, pulm. or cardiac failure, and complications of therapy
• Not all elevated CK’s are significant
• Don’t forget hypothyroidism can cause myopathies
• Not all myalgias are due to statins
• If statin myopathy continues despite stopping the statin, think about HMGCR Ab and statin induced autoimmune myositis
• IBM → distal + proximal muscle
• Think of anti- p155 Ab in cancer assc myositis
• Check anti-synthetase antibodies in patients with isolated idiopathic ILD
Asymptomatic hyper-CK-emia can be found with all of the following EXCEPT?

a. Normal physiology: male sex, race
b. Hypothyroidism
c. Hypogonadism
d. Muscle cramps
e. Ethanol use
66 y.o. diabetic white female on atorvastatin and metformin presented:
- severe muscle pain in her shoulders and hips
- morning stiffness 2 hours
- poor sleep
- Exam: mild limitation to B shoulder flexion and abduction and tenderness to B trochanteric bursae. No synovitis
- Labs: WBC 6.8, Hgb 10.1, Plt 448, Cr 0.9, CK 250 U/L aldolase 3.4 U/L (nl 1.0-7.5). ESR 40 mm/hr, CRP 2.1 mg/dL.

**What is the most appropriate next step?**

a. **Stop atorvastatin, repeat CK in 2-4 weeks**
b. **Switch atorvastatin to pravastatin**
c. **Order shoulder MRI to evaluate rotator cuff disease**
d. **Start prednisone 12.5-25 mg/day for polymyalgia rheumatica**
e. **Start pregabalin for fibromyalgia**
70 y.o. male with diabetes and HTN with:
- weakness for >6 months.
- difficulties with getting up from a seated position
- difficulties with combing his hair
- difficulties writing his name using a pen
Exam noted 4+/5 muscle strength L<<R side; he cannot maintain a grip against resistance.
Labs: CBC nl, Cr 1.15, AST 45, Alt 39, CPK 850, ESR 25.

What is the likely diagnosis?

a. Polymyositis
b. Polymyalgia rheumatica
c. Diabetic myonecrosis
d. Inclusion body myositis
e. Cerebrovascular accident (CVA)
55 y.o. female with hyperlipidemia and HTN on lovastatin and hydralazine:

- 2 months fatigue, weakness, and a pruritic rash (photo)
- 12 lbs unintentional weight loss X 2 month

Exam: Difficulties getting up from a seated position to move to the exam table. Enlarged L axillary lymph node and a mass on her L breast.

Labs: WBC 11.5, Hgb 10.8, plt 458, ESR 40, CPK 1750, aldolase 10.1, ANA 1:40 speckled pattern
What is the most likely diagnosis?

1. Statin induced myopathy
2. Systemic Lupus Erythematosus with myositis
3. Drug induced lupus
4. Paraneoplastic syndrome
5. Polymyositis
Question 5

Which of the following tests should be considered in a patient with idiopathic interstitial lung disease?

a. ANA
b. RF
c. Myositis (anti-synthetase) antibodies
d. ESR
e. ANCA