Anti-synthetase syndrome

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Disclosures

• I do not have any relevant financial disclosures.

• Off-label use:
  • Almost all medications discussed for treatment are not FDA-approved except for glucocorticoids.
Objectives

- Classification of myositis
- Definition of anti-synthetase syndrome
- Autoantibodies in anti-synthetase syndrome
- Different phenotypes
- Treatment
- Assessment of treatment response
- Prognosis
A patient.

• 1 year ago, a 53 year old woman was referred for treatment advice. Developed weakness in her arms and legs 2 years prior with a heliotrope rash and Gottron’s papules. CT scan revealed lung fibrosis. Labs showed a strongly positive Jo-1 antibody, confirming an anti-synthetase syndrome.

• She was short-winded on 3 liters of oxygen at rest, 4 liters during activity. She was on 25-30 mg of prednisone.

• Immunosuppressants tried: mycophenolate mofetil, azathioprine, rituximab.
A patient.

• She had difficulty getting out of her wheelchair.
• Her exam showed moderate weakness in most of her proximal muscles in arms/legs.
• Her fingers and toes were clubbed.
• She had a heliotrope rash over her eyelids and inflammatory rashes on her hands.
• Her lungs sounded coarse with crackles bilaterally.
• Her CT scan looked like this:
A patient.

What else can be done for her?
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Original Classification

Idiopathic Inflammatory Myopathies

- Polymyositis (PM)
- Dermatomyositis (DM)

Inclusion body (sIBM)

- Adult
- Juvenile
- Malignancy
- Overlap

Bohan et al. Medicine 56:255, 1977
PM/DM classification criteria

• Proximal muscle weakness
• Elevated serum skeletal muscle enzymes
• Myopathic changes on EMG
• Biopsy evidence of muscle inflammation
• Rash

• Definite PM or DM: 4 criteria satisfied
• Probable PM or DM: 3 criteria satisfied
• Possible PM or DM: 2 criteria satisfied

Bohan et al. Medicine 56:255, 1977
Distinguishing histologic features

**Polymyositis**
- Inflammatory infiltrate within fascicle & endomysial areas.
- Scattered or isolated necrotic fibers.

**Dermatomyositis**
- Perivascular infiltrate around fascicle.
- Perifascicular atrophy.
- Muscle microvasculature often involved.

http://www.neuro.wustl.edu/neuromuscular/pathol/inflammation.html
Newer Classification Paradigm

Autoimmune myositis

Overlap Myositis (OM)  DM  Necrotizing  PM  Sporadic IBM Autoimmune myositis (NAM)*

• CTD-associated myositis, i.e. SLE, scleroderma
• MDA-5-associated myositis
• Other myositis-specific/myositis-associated syndromes
• Anti-synthetase syndrome

*Also known as IMNM
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Definition of anti-synthetase syndrome

• 1. Presence of anti-synthetase antibody
• 2. Myositis (PM/DM)
• 3. Interstitial lung disease
• AND (Minor criteria)*
  • Raynaud’s phenomenon
  • Mechanics’ hands
  • Inflammatory arthritis
  • Fever (up to 1/3rd)

*Not all of these features may be present at baseline or ever

**Disease Epidemiology**

- Anti-synthetase syndrome first described in 1990 in 29 patients with PM/DM and ILD.

- Overall incidence of IIM is 6 to 10 per million, but incidence of Jo-1 + IIM ranges 1.2 to 2.5 per million and prevalence of 1.5 per 100,000.

- Average age at diagnosis is 50 years (22-74 years).

- Predominantly female, 2:1 ratio, may be higher in some series.

Love LA, Leff RL, Fraser DD et al. Medicine (Baltimore) 1991;70:360-74
Raynaud’s phenomenon
Mechanic’s hands

- Originally reported by Stahl et al. in 1979.
- Characterized by scaly fissures, hyperkeratotic skin abnormalities on lateral aspects of fingers (radial side of index fingers, commonly seen).
- Reported in up to 70% of anti-synthetase syndrome patients, often those who are Jo-1 with ILD.

“Mechanic’s Hands” (MH)
Inflammatory arthropathy

- Inflammatory arthritis “rheumatoid-like,” but negative anti-CCP antibodies.
- May be first manifestation of anti-synthetase syndrome in up to 27% of patients.
- Deforming subluxation of interphalangeal joints of thumbs and fingers.
- Periarticular calcifications may be present.
- Sometimes erosions seen at carpal bones, MCPs, and PIPs.

Disease Characteristics of ILD in anti-synthetase syndrome

• Shortness of breath and dry cough are common symptoms.

• Pulmonary function testing reveals restrictive physiology (i.e. FVC ≤ 80%).

• ILD subtype classified as non-specific interstitial pneumonia (NSIP)—most common, cryptogenic organizing pneumonia (COP), and usual interstitial pneumonia (UIP).

• Chest imaging shows basilar abnormalities: reticular and ground-glass opacities with loss of lung volume, traction bronchiectasis.
Interstitial Lung Disease
Interstitial Lung Disease
Disease characteristics of ILD patients

• Prevalence of ILD 67-100% in anti-synthetase syndrome.

• Onset of ILD variable: most of the time occurs concurrently at time of myositis diagnosis.

• Course ranges from acute and fulminant ILD, chronic progressive, or asymptomatic (subclinical).

• ILD leads to poor functional status with reduction in activities in 30% of patients.

ILD characteristics

ILD course in 66 Jo-1 + patients with median follow-up 36 months.

- Resolution: 17%
- Improvement: 24%
- Deterioration: 59%

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Concept of “Autoantibodies”

- Antibodies are produced by plasma cells (B cells) in immune system.
- Each antibody recognizes an antigen that is unique.
- Outcome: to successfully fight against viruses/bacteria.
- Autoantibodies: antibodies formed that are directed against self proteins
  - May be an innocent bystander (otherwise known as a “marker”)
  - Or may be pathogenic
Anti-synthetase antibodies

- These are antibodies directed against *aminoacyl-transfer RNA synthetases* (autoantibody target).
  - These enzymes catalyze binding of an amino acid to its tRNA in process of cytoplasmic protein synthesis.
- To date, there are 8 anti-synthetase antibodies.
- Anti-synthetase antibodies are mutually exclusive (usually).

## Anti-synthetase antibodies

<table>
<thead>
<tr>
<th>Antigen</th>
<th>tRNA synthetase</th>
<th>Frequency in adult PM (%)</th>
<th>Frequency in adult DM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Jo-1</strong></td>
<td>Histidyl</td>
<td>20-30</td>
<td>5-10</td>
</tr>
<tr>
<td><strong>PL7</strong></td>
<td>Threonyl</td>
<td>2-5</td>
<td>2-5</td>
</tr>
<tr>
<td><strong>PL12</strong></td>
<td>Alanyl</td>
<td>2-5</td>
<td>2-5</td>
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<tr>
<td>EJ</td>
<td>Glycyl</td>
<td>&lt;2</td>
<td>&lt;2</td>
</tr>
<tr>
<td>OJ</td>
<td>Isoleucyl</td>
<td>&lt;1-2</td>
<td>&lt;1-2</td>
</tr>
<tr>
<td>KS</td>
<td>Asparagynyl</td>
<td>&lt;1-2</td>
<td>&lt;1-2</td>
</tr>
<tr>
<td>Ha</td>
<td>Tyrosyl</td>
<td>&lt;1-2</td>
<td>&lt;1-2</td>
</tr>
<tr>
<td>Zo</td>
<td>Phenyalanyl</td>
<td>&lt;1-2</td>
<td>&lt;1-2</td>
</tr>
</tbody>
</table>

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Jo-1 + disease phenotype

• Most common and first to be described.
• May be pathogenic: activates components of immune system causing downstream inflammatory effects on tissues.
• More severe myositis presentation
  • Often have MH and other “typical” characteristics of the anti-synthetase syndrome: i.e., inflammatory arthritis, Raynaud’s, etc..

Jo-1+ disease phenotype

• 70-90% of Jo-1+ patients have ILD.

• Jo-1+ patients with ILD have mechanic’s hands and lower CK compared to Jo-+ without ILD.

• Jo-1 antibody titer may correlate with myositis disease activity and other organ system activity (i.e. lung, joints).

• Malignancy is rare in Jo-1+ positive patients, although has been reported. Protective?


Marie I, Josse S, Hatron PY, et Al. Arthritis Care & Research.2013;800-808
PL7 Phenotype

• Rarer than Jo-1, comprises 10-15% of anti-synthetase syndromes.
• Myositis is mild-moderate or not present at all.
• Raynaud’s, **pericardial effusion**, esophageal involvement, mechanics’ hands.
• Higher incidence of ILD, over 90% in some series.
  • ILD less likely asymptomatic, rarely resolves.
  • Marked ILD deterioration, poorer survival than Jo1+

PL12 phenotype

• Less common than Jo-1: 5-10% in anti-synthetase syndromes.

• Higher incidence of ILD (70-100%).
  • Most present with ILD concurrently with other anti-synthetase manifestations.
  • UIP pattern may be common compared to Jo-1.
  • ILD more severe in presentation and less likely to resolve, poorer survival than Jo-1+.

• Less than 50% of patients have muscle involvement (usually mild or subclinical).

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My approach to inflammatory myositis treatment

At baseline: does the patient have ILD?

- Yes
  - Assess for ILD severity
    - Mild-moderate
      - Pick therapies unlikely to exacerbate ILD
    - Severe
      - Proceed to intense Immunosuppressive therapy and assess for pulmonary arterial hypertension

- No
  - Assess for myositis severity
    - Mild-moderate
      - Proceed to intense Immunosuppressive therapy and assess for pulmonary arterial hypertension
    - Severe
      - Standard Therapy with “First-line” agents
Treatment: My approach.

• First line: Glucocorticoids + a steroid sparing agent:
  • Azathioprine (2 mg/kg) or mycophenolate mofetil (standard dosing, but may increase to 1500 mg twice daily).

• Glucocorticoid dosing: pulse intravenous daily (3 days) for severe disease (i.e. severe weakness, dysphagia, progressive ILD).

• Oral glucocorticoids with taper: 1 mg/kg for 4 weeks, taper by 2.5-5 mg every 2-4 weeks pending treatment response and tolerability.
  • Oral taper may slow or stop ~5-10 mg daily.
Treatment: My approach.

- Intravenous immunoglobulin (IVIG) may be used initially or as “bridge therapy” until maintenance immunosuppressives kick in.

- IVIG 1 gram/kg of IBW for 2 consecutive days once monthly for 1-3 months, or 3-6 months, or longer depending on response.
  - Some patients do not tolerate due to headaches, neurologic symptoms, meningitis at higher volumes.
  - Lower doses may be used.
Treatment: My approach for severe disease or progressive ILD

- **IV** (usually 0.7 to 1.0 g/m² for 6 mos.) or oral cyclophosphamide.
  - Data exists for improvement in Jo-1+ pts with ILD in small series of patients.

- **Cyclosporine** or **Tacrolimus**
  - Data exists in some small series of patients.
  - I have more experience with tacrolimus, twice daily dosing targeting a trough level of 5-10 ng/mL.
  - Monitor for hypertension, renal insufficiency, electrolyte derangements, peeling rashes.
Rituximab and myositis

- “RIM” trial of refractory juvenile/adult IIM, 83% met definition of improvement, some methodological concerns.

- In my experience: 2 different ways of dosing: 375 mg/m2 once a week X 4 weeks or 1000 mg X 2 (separated by 2 weeks)
  - Sometimes it works.

- Refractory IIM patients with strongly positive autoantibodies (i.e. Jo-1) may be more responsive to rituximab (shorter time to improvement).

- Interestingly, autoantibody titers may decrease after rituximab suggesting a correlation with clinical response.

I don’t use these medications/treatments for anti-synthetase syndrome

• Methotrexate, concern for exacerbation of ILD.
• Leflunomide, concern for exacerbation of ILD.
• Plasmapheresis.
• Never used: Acthar, abatacept, belimumab.
• Never used any of the TNF-inhibitors, concern for exacerbation of ILD.
If Reflux is present, treat.

- Emphasize lifestyle changes/conservative management with elevation of head of bed, avoidance of alcohol and smoking, no large meals late at night, etc…
- Treatment with proton pump inhibitors/H2 blockers.
- Uncontrolled GERD may affect underlying lung disease, i.e. “silent microaspiration,” may trigger cough and exacerbate underlying pulmonary disease.

Management of side effects and other concerns.

• Screen for latent TB, HIV, hepatitis B and C infections.

• Check vaccination status including influenza and pneumococcal vaccines.

• Screen for diabetes, hyperlipidemia, hypertension, osteoporosis at baseline.
Management of side effects and other concerns.

• Counsel women of childbearing age and recommend birth control as appropriate.

• Use PJP prophylaxis for all patients with ILD on immunosuppressives (expert opinion).

• Treat infectious complications, i.e. herpes zoster, influenza, pneumonias, as they arise and hold or reduce immunosuppressives if needed.
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My assessment of Treatment Response

• Improvement or stabilization of muscle strength.
• Normalization of muscle enzymes: CPK, aldolase, LDH, AST, ALT.
• May check serial EMGs or muscle MRIs.
• Improvement of other organ systems such as pulmonary:
  • Serial PFTs (≥10% in FVC and/or ≥15% in DLCO).
  • Serial chest imaging, preferably high resolution CT imaging.

Objectives

• Classification of myositis
• Definition of anti-synthetase syndrome
• Autoantibodies in anti-synthetase syndrome
• Differing clinical presentations among autoantibody subtypes
• Treatment
• Assessment of treatment response
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Prognosis

- **ILD** is the most important contributor to disease morbidity and mortality.
  - Severely reduced FVC and DLCO at presentation is a poor prognostic factor, portending lack of treatment response and deterioration.
  - UIP pattern, poorer prognosis.
  - Respiratory muscle involvement leads to faster deterioration.
  - Progressive ILD may occur in ~20-30% of patients.

Prognosis

• These are additional complications of anti-synthetase syndrome associated with higher morbidity and mortality.
  • Infectious pneumonias.
  • Aspiration pneumonias, especially if weak swallowing mechanism.
  • Secondary pulmonary arterial hypertension.
  • Ventilatory failure with increasing oxygen requirements.
Prognosis

- Historically, in early studies of IIM patients with ILD, 5 year survival rate 60% (similar to idiopathic pulmonary fibrosis).
- Yet, recent studies suggest survival rate has improved.
- In treated IIM patients, ILD resolves in 19% and improves in 55%.
- One study, after median of 53 mos. follow-up, 1 year survival (94.4%), 3 year survival (90.4%), 5 year survival 86.5%.
- Relapses are common, usually seen if disease treated with glucocorticoids alone.

Prognosis

- Among 43 patients who had myositis-associated UIP (14 of them with anti-synthetase syndrome) and 81 with idiopathic pulmonary fibrosis at Univ. of Pittsburg, 1985-2014
  - Median cumulative and event-free survival time in IPF was worse at 5.25/1.8 years compared to 16.2/10.8 years.
  - Respiratory failure was most common cause of death.

*Myositis-associated usual interstitial pneumonia has a better survival than idiopathic pulmonary fibrosis.*

Prognosis

- Among 202 Jo-1+ (122) and non-Jo-1 abs.(80) patients at Univ. of Pittsburg, 1985-2009
  - 5 and 10 year unadjusted cumulative survival: 90% and 70% for Jo-1 +.
  - 5 and 10 year unadjusted cumulative survival: 75% and 47% for non-Jo-1+.
  - Difference in survival partly attributed to delay in diagnosis in non-Jo1 patients.
  - Overall mortality rate was similar in 2 groups (29% vs. 38%).
Back to the patient.

• She returned recently. Oxygen requirements had increased.

• Treated with tacrolimus in addition to azathioprine for a year. Tolerated it well.

• The muscle weakness improved to a certain degree. The enzymes were normal now, but felt more fatigued. Could not walk several feet without stopping to rest.

• The rashes resolved.
Back to the patient.

Prognosis looks poor. What else can be done?
Back to the patient

• A right heart catheterization showed moderate pulmonary hypertension.

• Saw a cardiologist who recommended vasodilators: would provide “mixed results at best.”

• I suggested a trial of cyclophosphamide.

• I will try to arrange for consideration of a lung transplant with the pulmonologists.
Summary

• Anti-synthetase syndrome is an autoimmune myositis defined by an anti-synthetase antibody, inflammatory myositis, ILD and other associated features.

• There appears to be differences in phenotypes among anti-synthetase antibodies: Jo-1+ tend to have complete syndrome and non-Jo1 have predominant ILD.

• ILD is an important contributor to morbidity and survival (main cause of death).

• My treatment approach: combine steroids with another immunosuppressive based on severity of ILD.

• Prognosis seems to differ among autoantibody type, but appears better than patients who have idiopathic pulmonary fibrosis.
Questions & Discussion