Anti-synthetase syndrome

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Disclosures

• Octapharma: clinical trial support
• Genentech: clinical trial support
• Off-label use:
  • Almost all medications discussed here for treatment are not FDA-approved.
Objectives

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

- A 53 year old woman developed weakness in her arms and legs and rashes. CT scan revealed lung fibrosis. Labs showed a 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: steroids, mycophenolate mofetil, azathioprine, rituximab, tacrolimus.
A patient.

- She had difficulty getting out of her wheelchair.
- Her exam showed moderate to severe weakness in most of her proximal muscles in arms/legs.
- She had a 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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Traditional Classification

Idiopathic Inflammatory Myopathies

- Polymyositis (PM)
- Dermatomyositis (DM)

Inclusion body myositis (sIBM)

- Adult
- Juvenile
- Malignancy
-Overlap

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

- Symmetrical 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/fibrosis
- AND (Minor criteria)*
  - Raynaud’s phenomenon
  - Mechanic’s hands
  - Inflammatory arthritis
  - Fever (up to 1/3rd)

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

Disease Epidemiology

• First described in 1990 in 29 patients with PM/DM and ILD.

• Rare: 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.

• 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
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)

Downloaded with permission, ACR, 2018.
Inflammatory arthropathy

- Inflammatory arthritis “rheumatoid-like,” but negative anti-CCP antibodies.
- May be first manifestation of anti-synthetase syndrome in 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 a protein (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 IIM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jo-1</td>
<td>Histidyl</td>
<td>20-30</td>
</tr>
<tr>
<td>PL7</td>
<td>Threonyl</td>
<td>&lt;5</td>
</tr>
<tr>
<td>PL12</td>
<td>Alanyl</td>
<td>&lt;5</td>
</tr>
<tr>
<td>EJ</td>
<td>Glycyl</td>
<td>&lt;5</td>
</tr>
<tr>
<td>OJ</td>
<td>Isoleucyl</td>
<td>&lt;5</td>
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<tr>
<td>KS</td>
<td>Asparagynyl</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Ha</td>
<td>Tyrosyl</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Zo</td>
<td>Phenyalanyl</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

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Jo-1 + disease phenotype

• Most common and first to be described.
• Antibody may be pathogenic: activates components of immune system causing downstream inflammatory effects on tissues.
• Often have mechanic’s hands and other “typical” characteristics of the anti-synthetase syndrome: i.e., inflammatory arthritis, Raynaud’s, etc..
• Better survival than non-Jo-1 patients

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 disease activity and other organ system activity (i.e. lung, joints).
- Malignancy is rare in Jo-1+ positive patients, although has been reported. Protective?

PL7 Phenotype

• Rarer than Jo-1, comprises 10-15% of anti-synthetase syndromes.
• Myositis is mild or not present at all.
• Raynaud’s, pericardial effusion, esophageal involvement, mechanics’ hands.
• Higher incidence of ILD, over 90% in some series.
  • ILD is severe, 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

Standard Therapy with “First-line” agents

Severe

Proceed to intense immunosuppressive therapy

Mild

Standard Therapy with “First-line” agents

Severe

Proceed to intense immunosuppressive therapy

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
Treatment: My approach.

- First line: Glucocorticoids + a steroid sparing agent:
  - Azathioprine (2 mg/kg)
  - Mycophenolate mofetil
  - Methotrexate (if no severe ILD)

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

- Oral glucocorticoids with taper.
  - 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 1-2 gram/kg of ideal body weight.
  • Some patients do not tolerate due to headaches, neurologic symptoms at higher volumes.
  • Lower doses may be used.
Treatment: My approach for severe disease or progressive ILD

- IV 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 5-20 ng/mL.
  - Monitor for hypertension, renal insufficiency, electrolyte derangements, peeling rashes.

Rituximab and myositis

- “RIM” trial of refractory juvenile/adult IIM, didn’t meet endpoints, but 83% met definition of improvement.
- 2 different ways of dosing: 375 mg/m² once a week X 4 weeks or 1000 mg X 2 (separated by 2 weeks)
- Refractory IIM patients with strongly positive autoantibodies (i.e. Jo-1) may be more responsive to rituximab (shorter time to improvement).
- Interestingly, autoantibody titers decrease after rituximab suggesting a correlation with clinical response.

I don’t use these treatments with severe ILD

- Methotrexate.
- Leflunomide.
- Plasmapheresis.
- Although these have been used, I don’t have any experience: 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, Shingrix 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.
- Consider using pneumocystis 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
• Prognosis
Prognosis

• **ILD** is most important contributor to survival.
  • Severely reduced FVC and DLCO at presentation is 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

• 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, 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 treated only with glucocorticoids.

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

• Among 43 patients with myositis-associated UIP (14 with anti-synthetase syndrome) and 81 with idiopathic pulmonary fibrosis (IPF) at Univ. of Pittsburg, 1985-2014
  • Median cumulative and event-free survival time in IPF was worse.
  • 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: 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.
Back to the patient

- A right heart catheterization showed pulmonary hypertension.
- Saw a cardiologist who recommended vasodilators.
- She received a double lung transplant.
- Doing well this year.
Summary

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

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

- ILD is an important contributor to survival.

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

- Prognosis differs among autoantibody type, but appears better than in idiopathic pulmonary fibrosis.
Questions & Discussion