Lupus for the Internist: Advances in Internal Medicine 2016

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Outline

• Diagnosis and assessment
• Contraception
• Cardiovascular disease
• Vaccinations and infectious complications
• Advances in treatment

What is SLE?

• Autoimmune disease characterized by the production of autoantibodies
• Involvement of multiple organ systems
• Heterogeneous disease pattern
• Characterized by flares and periods of quiescence

Epidemiology of SLE

SLE prevalence ~1/1500 Americans
Diagnosis and Assessment

Case

• 27 year old woman presents with two months of erythematous rash on hands and joint pain
• Labs reveal mild lymphopenia, normal CRP, and elevated ESR
• ANA >1:640 speckled pattern
• C3 and C4 low

Choosing Wisely – ABIM/ACR

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Don't test ANA sub-serologies without a positive ANA and clinical suspicion of immune-mediated disease.

Tests for anti-nuclear antibody (ANA) sub-serologies (including antibodies to double-stranded DNA, Smith, RNP, SSA, SSB, Sci-70, centromere) are usually negative if the ANA is negative. Exceptions include anti-Jo1, which can be positive in some forms of myositis, or occasionally, anti-SSA, in the setting of lupus or Sjögren's syndrome. Broad testing of autoantibodies should be avoided; instead the choice of autoantibodies should be guided by the specific disease under consideration.


1997 ACR Classification Criteria

• Malar rash
• Discoid rash
• Photosensitivity
• Oral ulcers
• Arthritis
• Serositis
• Renal disorder
• Neurologic disorder
• Hematologic disorder: hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia
• Immunologic disorder: anti-dsDNA, anti-Sm, ACL IgG/IgM
• Anti-nuclear antibodies

Mucocutaneous
Internal organ
Lab
1. Malar Rash

2. Discoid Rash
3. Photosensitivity

4. Oral Ulcers

5. Arthritis
6. Serositis

7. Renal Disorder

8. Neurological Disorder

9. Hematologic disorder
   - Hemolytic anemia
   - Leukopenia (<4K)
   - Lymphopenia (<1.5K)
   - Thrombocytopenia (<100K)
10. Immunologic

- Anti-phospholipid antibody
- Anti-dsDNA
- Anti-Sm
- (False + test for syphilis)

11. Positive ANA

False positive rate in healthy controls: 3% (ANA 1:320) to 30% (ANA 1:40)

Case

- You refer your patient to rheumatology for a new diagnosis of lupus based on positive ANA, dsDNA, hypocomplementemia, leukopenia, specific lupus rash, and arthritis
- What other tests are critical in triaging this patient?

Lupus Nephritis

- ~30% of patients with SLE have evidence of nephritis at time of diagnosis
- Overall, prevalence of lupus nephritis is ~50-60% in first ten years after diagnosis
- Screen for renal involvement in ALL patients with lupus at time of diagnosis and in follow up with urinalysis and urine protein and urine creatinine (spot is fine)

Hahn, B. Arthritis Care & Research. 2012 June; 64(6): 797-808.
Case

• Her urinalysis reveals 1+ protein, 5-10 RBCs and spot UPCR is 0.7 g/g
• Does she need further work up for these findings?

Lupus Nephritis

• Indications for renal biopsy
  – Increasing serum Cr
  – Proteinuria ≥1.0 g per 24h
  – Proteinuria ≥0.5 g per 24h plus hematuria
  – Proteinuria ≥0.5 g per 24h plus cellular casts

Hahn, B. Arthritis Care & Research. 2012 June; 64(6): 797-808.

Case

Your patient is diagnosed with focal proliferative (class III) lupus nephritis and is started on Cellcept, prednisone, and hydroxychloroquine
6 months later, routine labs reveal a white blood cell count of 1.9K
You advise her to:
A. Stop Cellcept and recheck labs in 1-2 weeks
B. Increase prednisone to 20 mg
C. Stop hydroxychloroquine
D. Get blood cultures drawn

Lupus Flare versus Infection

<table>
<thead>
<tr>
<th>Lupus Flare</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia, thrombocytopenia</td>
<td>Leukocytosis, thrombocytosis</td>
</tr>
<tr>
<td>Normothermic</td>
<td>Fever, shaking chills</td>
</tr>
<tr>
<td>Elevated ESR, normal CRP</td>
<td>Elevated ESR and elevated CRP</td>
</tr>
<tr>
<td>Decreased C3 and C4</td>
<td>Unchanged C3 and C4 from prior</td>
</tr>
<tr>
<td>Increased dsDNA</td>
<td>Unchanged dsDNA from prior</td>
</tr>
<tr>
<td>Specific signs of lupus activity (e.g. arthritis, rash)</td>
<td>Localizing signs of infection</td>
</tr>
</tbody>
</table>
Case

- She is feeling well, with no evidence of infection or lupus activity. Her dsDNA and C3 levels are unchanged and platelet count and hematocrit are normal.

Case

- You advise her to:
  A. Stop Cellcept and recheck labs in 1-2 weeks
  B. Increase prednisone to 20 mg
  C. Stop hydroxychloroquine
  D. Get blood cultures drawn

Side Effects of SLE Treatments

<table>
<thead>
<tr>
<th>Medication</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Too numerous to list</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Retinal damage</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Liver damage, bone marrow suppression, infection</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Bone marrow suppression, infection</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Bone marrow suppression, infection</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Bone marrow suppression, infection</td>
</tr>
<tr>
<td>Belimumab</td>
<td>Infection, GI</td>
</tr>
</tbody>
</table>
Case
She returns to you for follow up and is not using contraception. She is sexually active with her husband. She asks you what you recommend for contraception.
You recommend:
A. Nuva-ring
B. IUD
C. Depo Provera
D. Need more information

Contraception and Lupus
• Fertility is preserved!
• Many of our patients are on teratogenic medications (Cellcept, ace inhibitors, etc)
• Patients with active SLE or significant end organ damage (e.g. CKD) are at increased risk for adverse outcomes during pregnancy
• Appropriate counseling about contraceptive methods is critical

Contraception and Lupus
• Antiphospholipid antibody status
  – APL antibodies include lupus anticoagulant, anti-cardiolipin IgG and IgM, and anti-beta-2 glycoprotein I IgG and IgM
  – APL positivity is a contraindication to estrogen-containing methods, regardless of whether patient has had previous thrombosis
  – Progestin-only or non-hormonal methods are recommended
• Effects on bone density
  – Concern about Depo Provera, especially in patients with chronic steroid exposure

Tedeschi S. Clin Rheumatol. 2016 May 11. [Epub ahead of print]
Case

- You recommend:
  A. Nuva-ring
  B. IUD
  C. Depo Provera
  D. Need more information

Cardiovascular Disease

Your patient presents to the ED with chest pain radiating to the neck. EKG shows ST depressions in the inferolateral leads. Her troponin is elevated.

What is the most likely cause of her cardiac ischemia?

- A. Myocarditis
- B. Coronary artery vasculitis
- C. Pericarditis
- D. Atherosclerotic coronary artery disease

Cardiovascular Disease and Lupus

CVD is a leading cause of mortality in patients with SLE
**Cardiovascular Disease and Lupus**

- All-cause mortality has declined in SLE has declined over the past 20 years, but the risk of death due to CVD remains unchanged.
- Management of traditional modifiable risk factors is important, but we do not how much this mitigates this risk.


**Cardiovascular Disease and Lupus**

- Traditional risk assessment tools underestimate risk of CVD in lupus patients.
- Modified Framingham risk score in which item is multiplied by 2 more accurately predicts CAD in patients with lupus.
- This may better highlight the population to target for intensive risk factor modification; however, we don’t know if acting on this multiplier risk calculation impacts outcomes.


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**Case**

- Your patient presents to the ED with chest pain radiating to the neck. EKG shows ST depressions in the inferolateral leads. Her troponin is elevated.
- What is the most likely cause of her cardiac ischemia?
  A. Myocarditis  
  B. Coronary artery vasculitis  
  C. Pericarditis  
  D. Atherosclerotic coronary artery disease

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**Vaccinations and Infectious Complications**
Case

• Your patient, who is on Cellcept, has read online that vaccines may not be safe for her to get. What do you tell her?

Vaccinations and Lupus

• Infections are a significant cause of death in lupus patients
• Strongly recommend annual inactivated flu vaccine, PCV13 (Prevnar), and PPSV23 (Pneumovax) in all patients on immunosuppression, regardless of age, according to ACIP guidelines
• Live vaccines should be avoided in patients on immunosuppressive medications

MMWR, October 12, 2012, Vol 61, #40

Invasive Pneumococcal Disease

Invasive Pneumococcal Disease (IPD) 10-40% fatality

Meningitis 6.3%
Bacteremia 19.2%
Pneumonia (NPD) 66.5%

Pneumococcus and Lupus

New ACIP/CDC/ACP 2015 Guidelines Recommend 2 Vaccines

Case

You receive a message from your patient:

“I’ve developed a painful rash and I’m worried it may be due to lupus.”

Zoster and Lupus


Zoster and Lupus

Yun, H. Arthritis and Rheumatology. 2016 Mar 18. [Epub ahead of print]
Case

- Your patient asks you if you’ve heard anything about the lupus medication she has seen commercials about on TV. She thinks it starts with a “B”.

B-cell targeted therapy

- Belimumab
- Rituximab
- Multiple other drugs in various phases of investigation
Belimumab for the Treatment of Lupus

Belimumab is the first medication approved for the treatment of lupus in 50 years. Its effect is modest and primarily seen in mucocutaneous and joint disease. There is no role in the treatment of organ-threatening lupus. Main side effects are GI and infection.

Furie, R. Arthritis and Rheumatism. 2011 Dec; 63(12): 3918-3330.


Rituximab for the Treatment of Lupus

Two RCTs in patients with moderate to severe lupus (EXPLORER) and patients with class III/I lupus nephritis (LUNAR) did not meet their primary endpoints.

However, there were significant issues with trial design, populations recruited, choice of endpoints, etc. Many centers, including ours, have had good success in using rituximab off-label in patients with refractory lupus nephritis.


Rovin, B. Arthritis and Rheumatism. 2012 Apr; 64(4): 1215-1226.

Summary

- Check ANA and subserologies only in appropriate clinic setting, not for diffuse pain or fatigue without other objective clinical evidence of disease
- Screen for lupus nephritis in all patients at diagnosis and in follow up with UA and UPCR
- Contraception is critical – remember APL and bone density considerations
- Most common side effects of many medications used to treat SLE are bone marrow suppression and infection
- Cardiovascular disease is a leading cause of mortality in SLE patients
- Vaccinate SLE patients against S. pneumoniae with both PCV13 and PPSV23
- Zoster incidence appears to rising, prevention currently limited by ability to administer live vaccine to our patients