Lupus and the heart

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Premature Atherosclerotic Cardiovascular Disease in Systemic Lupus Erythematosus

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Case

- 39 year old with SLE presents to the Emergency Department with chest pain and shortness of breath.
- She is evaluated by the Emergency physician who takes a history, examines her and orders some tests, including an EKG.
- The EKG shows sinus tachycardia (rapid heart rate) and ST elevations in some of the pre-cordial leads.
- The patient’s oxygen level is OK. The pain has subsided.
The ED physician assumes that the patient has a lupus flare with pleurisy.

The ED physician gives the patient a prescription for a medrol dose pack and discharges the patient.

The patient has recurrent chest pain and returns to the Emergency Department the next day.

She is diagnosed with a heart attack.
Premature Atherosclerotic Cardiovascular Disease in Systemic Lupus Erythematosus

- Why should we understand Lupus and heart disease?
- Because it can affect our loved ones with Lupus!
ASCVD in Women

- Coronary Heart Disease is the leading cause of death in women
- Deaths due to cardiovascular disease are increasing in American women despite advances in prevention and therapy
- Women have higher mortality rates and are less likely to receive standard interventions after myocardial infarction than men

Systemic Lupus Erythematosus

SLE - A Spectrum of Disease

Mild
Moderate
Severe
Bimodal Mortality of SLE

**Early mortality:** Kidney Disease, Central nervous system disease, Infection

**Late Mortality:** Cardiac and Cerebrovascular Events

Cardiovascular Mortality of SLE

Even after adjusting for the traditional Framingham risk factors, the relative risk of coronary artery disease with SLE is high.

SLE is an independent risk factor for cardiovascular events

Manzi et al, Am J Epidemiol, 1997; 145: 408-415
Atherosclerotic Plaque Development

- Normal
- Early
- Lipid rich
- Internal rupture
- Calcified shell
- Calcified plaque
- Vulnerable
- Rupture
- Thrombus
- Myocardial infarction
- Obstructive

- Fatty streaks
- White blood cells
- Red blood cells
- Calcium
- Lipid rich plaque
- Scar
- White blood cells
- Platelets and fibrin

Inflammation and calcification

Scar development with calcification
Formation of an Advanced, Complicated Lesion of Atherosclerosis

Macrophage accumulation  Formation of necrotic core  Fibrous-cap formation

Vulnerable Plaque Rupture

- Systemic inflammation causes the fibrous cap to be thinned with decreased smooth muscle cell synthesis and increased collagen breakdown.
Unstable Fibrous Plaques in Atherosclerosis

Measurement of Atherosclerosis

- Direct measures
  - Heart attacks, strokes or death
- Indirect Measures
  - Coronary artery calcification
  - Carotid artery ultrasound changes
Prevalence of Atherosclerotic Plaque Among Control Subjects and Patients With SLE According to Decade of Life

Roman MJ et al. NEJM 2003; 349: 2399-2406
CAC in SLE patients and Controls in different age groups

## Characteristics of SLE patients with and without CAC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CAC Positive</th>
<th>CAC Negative</th>
<th>P (Unadjusted)</th>
<th>P (Age Adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>45</td>
<td>107</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Disease (yrs): Mean (SD)</td>
<td>15.7 (9.6)</td>
<td>9.1 (7.2)</td>
<td>&lt;0.0001</td>
<td>0.0050</td>
</tr>
<tr>
<td>Systolic BP: Mean (SD)</td>
<td>129.8 (16.3)</td>
<td>120.3 (14.3)</td>
<td>0.0011</td>
<td>0.20</td>
</tr>
<tr>
<td>Diastolic BP: Mean (SD)</td>
<td>76.5 (9.2)</td>
<td>77.0 (10.2)</td>
<td>0.74</td>
<td>0.76</td>
</tr>
<tr>
<td>Post menopausal: n (%)</td>
<td>29 (64.4)</td>
<td>33 (30.8)</td>
<td>0.0002</td>
<td>0.53</td>
</tr>
<tr>
<td>Current Smokers: n (%)</td>
<td>12 (27.3)</td>
<td>19 (17.9)</td>
<td>0.20</td>
<td>0.072</td>
</tr>
<tr>
<td>Hcy (µmol/L): Mean (SD)</td>
<td>14.0 (4.8)</td>
<td>11.0 (4.1)</td>
<td>0.001</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Premature ASCVD in SLE Identification by EBCT

Results

Homocysteine (Hcy) was significantly greater in SLE patients than controls \( (p<0.0001) \), and higher in SLE patients with CAC than those patients without CAC \( (p<0.002) \). Therefore, Hcy is an inexpensive marker that can identify SLE patients at risk of ASCVD.

Premature ASCVD in SLE

Are the same factors associated with the presence of premature ASCVD in SLE patients, associated with progression of ASCVD?
Comparison of baseline and followup carotid ultrasound study results in 158 SLE patients

Rates of atherosclerosis progression by tertile of homocysteine concentration


I = 5.8 moles/liter, II = 5.9-7.8 moles/liter, and III = 7.9 moles/liter

P=0.001
Premature ASCVD in SLE

Therefore, Hcy is associated with progression of ASCVD carotid plaque.
Endothelial Cell Dysfunction

- The initial factor in atheroma formation is thought to be endothelial cell injury or dysfunction.

- In patients with ASCVD there is:
  - abnormal vascular repair
  - decreased pro-angiogenic cells

Tepper et al, Circulation 2002; 106:2781-2786
Denny et al., Blood 2007; 110:2907-2915
Pro-angiogenic Cells in SLE

- Pro-angiogenic cells are decreased and abnormal in SLE patients.

Denny et al., Blood 2007; 110:2907-2915
Proangiogenic cells in SLE patients & Controls

- Total number of pro-angiogenic cells (PACs) per mL in healthy controls, patients with SLE without CAC, and patients with SLE with >75th percentile CAC for age.
Progenitor cells in SLE patients & Controls

- Total number of progenitor cells (PCs) per mL in healthy controls, patients with SLE without CAC, and patients with SLE with >75th percentile CAC for age
Are circulating pro-angiogenic cells reduced in patients with SLE independent of ASCVD

Conclusion
Our study is the first to show that reduced numbers of ProAngiogenic Cells in SLE patients may be observed even in the absence of coronary calcification. Depletion of total circulating PCs does not appear to fully explain this difference.
ASCVD in SLE

What should we do with all this information?
SLE Therapy

Education
Rest
Sun Avoidance/Sunscreens
Antimalarials
NSAID’s
DHEA
Corticosteroids
Immunosuppressive Agents
Biologics
Who is Managing the cardiovascular risk in SLE patients?

Everyone!

Patient and Family
Primary Care Physician
Rheumatologist
Nephrologist if applicable
Cardiologist if applicable
Avoid Flares!

- Adherence to medication regimen
- Avoid Environmental triggers
Take care of your health!

- Tight control of blood pressure
- Statins if indicated
- Exercise
- Keep a healthy weight
Sun Avoidance

- Avoid direct sun exposure
  - Sun-block – UV-A and UV-B
- Fluorescent Lights (indoor exposure)
- Avoid Tanning Salons
SLE Therapy

- Rest
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- Biologics
SLE Therapy

Anti-malarial Agents

Hydroxychloroquine
Chloroquine
Quinacrine
Effect of antimalarials on thrombosis and survival in SLE

- Prospective cohort 232 patients with SLE
- Taking antimalarials was protective against thrombosis (HR 0.28, 95%CI 0.08–0.90)
- Twenty-three patients died, 19 of whom (83%) had never received antimalarials.
- No patient treated with antimalarials died of cardiovascular complications. Cumulative 15-year survival rates were 0.68 for never versus 0.95 for ever treated patients (p< 0.001).

Effect of antimalarials on thrombosis & survival in SLE

**Figure 2** Kaplan–Meier survival curves by treatment group.

Systemic Lupus Erythematosus

Therapy

Rest
Sun Avoidance/Sunscreens
Antimalarials
NSAID’s
Corticosteroids
Immunosuppressive Agents
Biologics
SLE Therapy

NSAID’s

Lower risk of thromboembolic cardiovascular events with naproxen among patients with RA

Watson et al, Arch Int Med 2002; 162:1105-10

Increased risk of myocardial infarction in patients with RA taking Rofecoxib

Bombardier et al, NEJM 2000; 343:1520-8
Treating pain and minor symptoms

- Tylenol – safe option, often ineffective
- NSAIDs – careful use with steroids, coumadin
  » - trial and error
  » Topical therapies (diclofenac gel)
- Tramadol –
- Flexeril – can be helpful for MSK pains
- Opioids – last resort – slippery slope
  » Can be hard to control/ regulate
Systemic Lupus Erythematosus

Therapy

- Rest
- Sun Avoidance/Sunscreens
- Antimalarials
- NSAID’s
- Corticosteroids
- Immunosuppressive Agents
- Biologics
SLE Therapy

Corticosteroid use
Although in some studies corticosteroid use has correlated with premature ASCVD events in SLE patients, it is impossible to separate severity of disease from corticosteroid use.
Corticosteroid use

Corticosteroids can induce hypercholesterolemia and predispose to other cardiac risk factors including diabetes, hypertension, weight gain, etc.
Steroid Tips

- Set a timetable for use and clear goal
- Avoid use as “treatment” of disease
- Explain to patient reasoning for use
- Limit chronic use
- Warn against patient self-direction of use
- Taper when possible
Systemic Lupus Erythematosus

Therapy

Rest
Sun Avoidance/Sunscreens
Antimalarials
NSAID’s
Corticosteroids
Immunosuppressive Agents
Biologics
SLE Therapy

Immunosuppressive Therapy

Methotrexate
Azathioprine
Cyclosporin
Mycophenolate Mofetil
Cyclophosphamide
Systemic Lupus Erythematosus

Therapy

Rest
Sun Avoidance/Sunscreens
Antimalarials
NSAID’s
Corticosteroids
Immunosuppressive Agents
Biologics
SLE Therapy

Biologics

Rituximab
Belimumab
SLE Therapy

Immunosuppressive Therapy and Biologics in the treatment of Lupus is now being studied for their effect on cardiovascular disease.
What about alternative medicines?
Multitargeting by turmeric, the golden spice: From kitchen to clinic

Molecular Nutrition & Food Research
Volume 57, Issue 9, pages 1510-1528, 13 AUG 2012 DOI: 10.1002/mnfr.201100741
Premature ASCVD in SLE

- Premature ASCVD in SLE is likely attributable to consequences of inflammation
How do we manage cardiovascular risk in SLE

- Aggressive intervention of known risk factors: smoking, hypertension, hyperglycemia, obesity
- Aggressive use of lipid lowering agents
- Use biomarkers to identify patients at risk—such as Homocysteine levels
- Screen for coronary artery disease when indicated

Vaarala; Lupus; 9: 202-205. 2000
How do we manage cardiovascular risk in SLE

- Antiphospholipid Antibody Screening
- Prompt use of Steroid Sparing Agents
- Hydroxychloroquine use in all patients

Vaarala; Lupus; 9: 202-205. 2000