Lupus and the heart



Lupus Foundation of America Teleconference FEB 2015

Premature Atherosclerotic Cardiovascular Disease in Systemic Lupus Erythematosus

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- 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.

Case continued

- 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

MillerA & Oparil S Secondary Prevention of Coronary Heart Disease in Women: A Call to Action; Ann Intern Med. 2002; 138: 150-151

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

Urowitz MB et al, The bimodal mortality pattern of SLE. Am J Med 1976; 60: 221-225

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



Endothelial Dysfunction in Atherosclerosis



Ross R. N Engl J Med 1999;340:115-126



Formation of an Advanced, Complicated Lesion of Atherosclerosis



Ross R. N Engl J Med 1999;340:115-126



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



Ross R. N Engl J Med 1999;340:115-126



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



Von Feldt JM, et al. Arthritis Rheum. 2006 Jul;54(7):2220-7

Characteristics of SLE patients with and without CAC

Characteristic	CAC	CAC	P	P (Age
	Positive	Negative	(Unadjusted)	Adjusted)
	45	407	ND	
n	45	107	ND	ND
Disease (yrs): Mean(SD)	15.7 (9.6)	9.1 (7.2)	<0.0001	0.0050
Systolic BP: Mean (SD)	129.8 (16.3)	120.3 (14.3)	0.0011	0.20
Diastolic BP: Mean (SD)	76.5 (9.2)	77.0 (10.2)	0.74	0.76
Post menopausal: n (%)	29 (64.4)	33 (30.8)	0.0002	0.53
Current Smokers: n (%)	10 (07 0)	10 (17 0)	0.20	0.072
	12 (27.3)	19 (17.9)	0.20	0.072
Hcy (µmol/L): Mean	14.0 (4.8)	11.0 (4.1)	0.001	0.002
(SD)				

Premature ASCVD in SLE Identification by EBCT

<u>Results</u>

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

Von Feldt JM, et al. Arthritis Rheum. 2006 Jul;54(7):2220-7

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



Roman MJ, Crow MK, Lockshin MD, Devereux RB, Paget SA, Sammaritano L, Levine DM, Davis A, Salmon JE. Rate and determinants of progression of atherosclerosis in systemic lupus erythematosus. Arthritis Rheum. 2007 Oct;56(10):3412-9

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

Roman MJ, Crow MK, Lockshin MD, Devereux RB, Paget SA, Sammaritano L, Levine DM, Davis A, Salmon JE. Rate and determinants of progression of atherosclerosis in systemic lupus erythematosus. Arthritis Rheum. 2007 Oct;56(10):3412-9

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

Tepper et al, Ciculation 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 Sun Avoidance/Sunscreens Antimalarials NSAID's DHEA Corticosteroids **Immunosuppressive Agents 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 15year 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.

Ruiz-Irastorza et al, Lupus (2006) 15, 577-583

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.

SLE Therapy

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



Volume 57. Issue 9. pages 1510-1528, 13 AUG 2012 DOI: 10.1002/mnfr.201100741 http://onlinelibrary.wiley.com/doi/10.1002/mnfr.201100741/full#mnfr1798-fig-0001

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

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

Vaarala; Lupus; 9: 202-205. 2000

