Lupus, You and Primary Health Care.

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Objectives

• Learning how and when to suspect lupus.
• Appreciating the ongoing role of the Primary Care Provider in Lupus.
• Understanding the importance of non-autoimmune immune mediated aspects of lupus
Nomenclature

• The term *lupus*, was first used as a medical term
  o In 1230 by Rogerius Frugardi
  o In 1611 by Sennert

• *Lupus érythèmeateux* as a medical condition was coined in
  o 1833 by Pierre Cazenave

• The term *systemic lupus erythematosus* (SLE) was first used between 1895 and 1903.
Importance of Primary Care

- Lupus is the great imitator and masquerader.
- Patients have limited access to specialists.
- Many times specialist rely on their Primary Care Physicians (PCP’s) to care out plans.
- Patients survive longer and have an increased risk of chronic illnesses.
  - Hypertension
  - Hyperlipidemia
  - Cardiovascular disease
The Great Imitator

- Multiple sclerosis
- Interstitial lung disease
- Inflammatory bowel disease
- Type I Diabetes
- Autoimmune thyroid disease
- Idiopathic thrombocytopenia
- Antibody negative vasculitis
Common Symptoms

• 60% or more of patients have skin and/or joint manifestations at presentation.
  - Facial rash or sensitivity to sun
  - Lupus arthritis (not just joint pain)
• Proteinuria
• Cytopenia
• Recurrent/unusually severe thrombosis.
• Pleurisy or pneumonitis of unclear etiology.
• Pericarditis, congestive heart failure.
# Commonest Findings In Lupus

Frequency (%) of clinical symptoms in new onset lupus

<table>
<thead>
<tr>
<th>System</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>Musculoskeletal</td>
<td>57.1</td>
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<tr>
<td>Constitutional</td>
<td>50</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>50</td>
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<tr>
<td>Hematology</td>
<td>38.9</td>
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<tr>
<td>Renal</td>
<td>28.6</td>
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<tr>
<td>Cardiorespiratory</td>
<td>17.8</td>
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<tr>
<td>Neuropsychiatry</td>
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</table>

Frequency (%) of serological findings in new onset lupus

<table>
<thead>
<tr>
<th>Immunology</th>
<th>Frequency (5)</th>
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<tbody>
<tr>
<td>ANA</td>
<td>100</td>
</tr>
<tr>
<td>ds-DNA</td>
<td>83.6</td>
</tr>
<tr>
<td>Low C3</td>
<td>51.8</td>
</tr>
<tr>
<td>Low C4</td>
<td>49.5</td>
</tr>
<tr>
<td>SSA</td>
<td>28</td>
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<tr>
<td>aCL/β2GP/LA</td>
<td>24/17.2/16.3</td>
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<tr>
<td>Sm</td>
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Causes of a Positive ANA?

• Pre-clinical disease
• Non-rheumatologic ANA related disease
  o Autoimmune liver disease
  o Autoimmune thyroid disease
• Transiently Positive ANA
  o Post viral: HIV, Hep C, EBV
  o Drugs: Tetracycline
• Lab variability
• Non-pathogenic ANA (Fibro ANA)
  o Antibody to Dense Fine Speckled 70 Anti-gene
Primary Care practices serve the medical needs of your family and are able to provide care that is continuous, comprehensive and coordinated.
Undifferentiated Connective Tissue Disease (UCTD)

- UCTD is the preferred term for people not meeting the SLE criteria.
- Many of these patients never develop lupus.
- The ACR criteria can be used reliably to make a presumptive diagnosis of SLE.
- A negative ANA IF test essentially rules out SLE.
- If lupus is clinically suspected in an ANA negative patient, an SSA test may be helpful.
Education

• SLE management requires a physician-patient relationship
  - PCP
  - Rheumatologist
• Denial of their illness.
• Non-adherence with medications.
• Insurance problems
  - Uninsured
  - Underinsured
  - Patient support and resources.
Cardiovascular Disease (CAD)

- SLE patients have
  - A higher rate of atherosclerosis
  - A higher rates of progression atherosclerosis
  - A higher rate of subclinical atherosclerosis

- At least 13% of SLE patients have symptomatic atherosclerotic lesions

- Major cardiovascular complications in SLE
  - Myocarditis (heart disease)
  - Valvular disease
  - Endocarditis (infections)
  - Arrhythmias (rate and rhythm)
• Atherosclerosis has a significant immune and inflammatory component.
• Elevated C3 & White Blood Cell count (WBC) is seen in SLE with atherosclerosis.
• Things associated with cardiovascular events
  o Low-grade inflammation
  o Oxidative stress
  o Lipid peroxidation
Atherosclerosis

- Adaptive immunity is involved in atherosclerosis.
- T cells have a pathogenic role to atherosclerosis.
- T-helper (T\textsubscript{H})-1 cells contribute to atherosclerosis.
- T regulatory cells play a protective role against atherosclerosis and inflammation.
- B cells produce protective antibodies against oxidized LDL cholesterol.
Inflammation and CAD

- Obesity
- Diabetes mellitus
- SLE/aPL
- Hyperhomocysteinemia
- Hypercholesterolemia
- Reactive Oxygen Species
- Vitamin E
- Enhanced lipid peroxidation
- Arachidonic acid
- 8-iso-PGF$_{2\alpha}$ and other bioactive isoeicosanoids
- Platelet/coagulative activation
- Atherothrombosis
Fat Cells & Immunity

- Fat cells produce cytokines
  - TNF-α
  - IL 1 and 6

- TNF-α
  - Increases IL-6 and IFN-α over-expression
  - Hypertriglyceridemia/Dyslipidemia
  - Inflammation related to atherosclerosis

- Inflammatory is seen in SLE and the following
  - Obesity
  - Hypercholesterolemia
  - Type 2 diabetes mellitus
  - Homozygous homocystinuria
Other Risk Factors

• SLE causes complications that also cause heart disease.

• Extra-cardiac risk
  o Kidney disease (lupus nephritis)
  o Strokes
  o Pulmonary artery hypertension (PAH)
  o Peripheral artery disease (PAD)
  o Pericarditis

• Lupus also causes abnormal tests that are related to heart disease.
  o C-reactive protein (CRP)
Preventive Strategies

• Smoking cessation
• Regular physical activity
• Managing metabolic abnormalities
  o Dyslipidemia
  o Insulin resistance, and diabetes
  o Persistent disease activity
  o Minimizing exposure to corticosteroids
• Vitamin D supplementation
• Anti-malarials
• Low-dose aspirin
• Angiotensin-converting enzyme (ACE) inhibitors
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Hypertension (HTN)

- Hypertension has an immune-mediated causes.
- Chronic immune activation causes
  - Generation of oxygen free radicals
  - Resulting in oxidative stress
- Renal oxidative stress
  - Plays a role in immune-mediated hypertension.
  - Has hypertensive actions on renal vascular and tubular function.
- HTN is seen in Lupus knockout mice
  - Develop hypertension associated with renal oxidative stress.
Flow Diagram Depicting Possible Pathways That Promote SLE Hypertension

Am J Physiol Regul Integr Comp Physiol 2009;296:R1258-R1267
HTN In SLE

- Even patients with active non-kidney SLE have a higher rates of HTN.
- HTN is associated with serologically active SLE
- Active SLE has a higher interleukin (IL)-12/IL-4 ratio.
- Protein oxidation is higher in patients with active SLE.
- HTN is associated with an increased $T_\text{H}1/T_\text{H}2$ ratio and oxidative stress.
- There is an association between HTN and levels of
  - Glucose
  - Insulin
  - Hydroperoxides
  - IFN-γ
  - IL-17
  - IL-12/IL-10
  - Adiponectin
Dyslipidemia

- High prevalence of dyslipidemia noted in LN.
- Dyslipidemia is more common in renal impairment.
- Even in inactive SLE, dyslipidemia is more severe.
- Steroid use is associated with higher cholesterol levels.
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Pregnancy In Lupus

• Mother
  o Lupus activity

• Placenta
  o Pre-eclampsia/eclampsia/HELLP syndrome
  o Antiphospholipid syndrome

• Baby
  o Neonatal lupus
  o Risk of ANA positivity
  o Learning difficulties
  o Risk of development of lupus
Pregnancy and Lupus

- Pregnancy is least likely to be associated with a flare if
  - Mother has been in a remission for 6 months or greater
  - With HCQ use
- Pregnancy is most likely to be associated with a flare if
  - Active renal disease
- Pregnancy increases the risk of lupus exacerbations in the third trimester and postpartum period.
Antibodies in Pregnancy

• Antibodies that cross the placenta
  o SSA
  o SSB
  o U1RNP.

• Antiphospholipid antibodies (APS).
  o 40% of patients with SLE have these antibodies
  o 50% of those patients experience thromboembolism
  o Increase risk of fetal loss
Neonatal Lupus (NLS)

- NLS symptoms
  - Skin rash (with 2 months of birth)
  - Hematological symptoms
  - Liver or Cardiac symptoms
- Skin rash is seen in 15% and are transient.
- Complete heat block (CHB) rate is 1-2%.
- CHB is irreversible and associated with morbidity and a mortality of 18%.
- A pacemaker are implanted in 2/3 of cases.
- Maternal use of HQC reduces CHB.
Neonatal Lupus Syndrome

Third-degree heart block: P waves (red arrows) independent of the QRS complexes (blue arrows).
Treatment of Cutaneous NLE

- Reduced sun exposure
- Use protective clothing
- Use sunscreen
- Topic hydrocortisone
- Time heals all wounds (by 6 months)
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Lupus and Infections

- Lupus patients have a higher risk of infections
- Steroids increase the risk of infections
- Immunosuppressive medications used in SLE increases the risk of infections
- Infections increase the risk of SLE flares.
- SLE flares increase the risk of infections.
Infectious Hospitalization

![Graphs showing trends in infection rates over years](image)

**A.** Adjusted infection rate (%)

- Pneumonia
- UTI
- Opportunistic
- Sepsis
- Skin

**B.** Adjusted infection rate (%)

**C.** Incidence Rate Ratio

Teletonidou et al. A. C & R 67: 8, 2015, pp 1078–1085
Immunizations

- Vaccination should be avoided in active disease
- Vaccines are effective and safe in SLE
- Vaccines are best given prior to immunosuppressive therapy is started.
- Anti-malarials are known to be protective against infection
# Immunizations

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<td><strong>While</strong></td>
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Vitamin D

- It is a steroid hormone.
- Vitamin D has immune benefits.
- Vitamin D deficiency is more common in active SLE.
- Vitamin D deficiency is association with dyslipidemia, so may be related to heart disease.
- Vitamin D levels are inversely related with atherosclerotic plaque size so may be related to heart disease.
Actions of Vitamin D

- Renin-angiotensin system
  - ↓ B-type natriuretic peptide
- Vascular relaxation
- Insulin resistance
- Vascular calcification
- Vascular smooth muscle cell proliferation
- Platelet aggregation
- Tissue factor
  - ↓ PAI-1
  - ↑ Thrombomodulin
- NF-kappa beta
  - ↓ TGF-beta 1
  - ↓ TNF-alpha
Vitamin D and SLE

- Vitamin D has an inhibitory effect on abnormalities seen with SLE.
- Vitamin D values of < 20 ng/mL is associated with higher serum IFN-α & higher levels of activated B-cell.
- Replacement of Vitamin D decreases levels of memory B cells and anti-DNA antibodies.
- Vitamin D inhibit expression of SLE related inducible genes.
Vitamin D and SLE

- 29% of African American African patients have serum vitamin D levels < 10 ng/mL.
  - Photosensitive rash
  - Renal disease
- “Immuno-nutrition” is plagued with difficulties
  - Race
  - Ubiquitous in nature
  - Nutrition
  - Environmental
  - Medication induced: corticosteroid and phenytoin

Vitamin D & Osteoporosis

- Corticosteroid and osteoporosis
- Bisphosphonates and corticosteroids
- Vitamin D and Osteoporosis
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Mood Disorder (MD)

- Mood disorders are the second most frequent neuropsychiatric event in patients with SLE.
- Mood disorders have a negative impact on health-related quality of life.
- There is no relationship between MD and SLE activity, organ damage and lupus autoantibodies.
Antibodies and MD

- Serum IL1 and TNF α levels are associated with SLE mood disorders.
- Serum antibodies to N-methyl-D-aspartate (NMDA) receptor (anti-NR2) are associated with depression.
- 1/3 of lupus patients have fibromyalgia.
Fatigue

• Seen in 50-80% of patients with SLE
• Fatigue does not correlate with SLE serological or clinical activity.
• Fatigue highly correlated with the fibromyalgia
  o Pain
  o Depression
  o Sleep abnormalities
  o Poor quality of life2-5
• Fatigue is also associated with reduced physical fitness
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Cancer

• The data shows an association between SLE and malignancy

• There is an increased risk for the following
  o Hodgkin's lymphoma (HL)
  o Leukemia
  o Laryngeal carcinoma
  o Lung carcinoma
  o Some liver, vaginal/vulvar, and thyroid malignancies

• There is a reduced risk of the following in SLE
  o Skin melanoma
In Summary

• Communication
  o Between doctors
  o Between doctor and patient

• Early diagnosis and early referral

• Infection
  o Early detection, treatment and prevention

• Metabolic syndrome
  o Monitoring
  o Side effects from prednisone
  o Early onset CADx

• Cancer surveillance