Systemic Lupus Erythematosus (SLE)

- A chronic auto-immune disease
- Can affect multiple organ systems as a result of immune system dysregulation
- The cause is not exactly known but is felt to be multifactorial including genetic, environmental, age, sex and ethnicity
- Environmental triggers include ultraviolet light, sun exposure, medications and perhaps infections
SLE Epidemiology

- An estimated 51 per 100,000 people with lupus live in the United States
- Every year 2-8 cases per 100,000 people are diagnosed with lupus in North America, Europe and South America
- Most common in Asians, blacks and Hispanics with a peak incidence ages 15-44 but can occur in young children and the elderly
- Is 9-10 times more common in women suggesting that hormones could be a trigger and disease onset can occur at menarche, after or during a pregnancy or at menopause

SLE Epidemiology (cont)

- Siblings of patients with lupus are 30 times more likely to develop lupus but unrelated household contacts are also at risk suggesting an environmental trigger
- In the 1950s when it was very difficult to make a diagnosis of lupus early in the disease course, the 10 year survival was 50% but by 2000 the 10 year survival was over 90%
- The increase in survival rate is probably related to earlier disease diagnosis and a few newer therapies

SLE Diagnosis

- The diagnosis of lupus is made on the basis of history, physical exam and laboratory studies
- A positive ANA does not mean that a patient necessarily has lupus
- Because lupus can be difficult to diagnose, the Systemic Lupus International Collaborating Clinics (SLICC) group developed guidelines in 2012 to help clinicians make an accurate diagnosis of lupus
- The criteria are cumulative and need not be present concurrently so an accurate history is imperative
SLE Diagnosis (cont)

- A patient can be diagnosed with lupus if she/he has at least four criteria, including one clinical and one immunologic criteria or has confirmed lupus nephritis on a renal biopsy with a positive ANA and/or positive double-stranded DNA antibodies
- Clinical criteria include
  - acute cutaneous lupus - malar rash, photosensitive rash, bullous lupus, maculopapular rash, toxic epidermal necrolysis or subacute cutaneous lupus (non-indurated psoriaform and/or polycystic lesions) that may require a skin biopsy for dx

SLICC clinical criteria (cont)

- Chronic cutaneous lupus - discoid rash (scarring with increased pigmentation in light skinned individuals and decreased pigmentation in dark-skinned individuals), hypertrophic (venerous) lupus, lupus panniculitis (also called profundus), mucosal lupus, lupus erythematosus tumidus, chilblains lupus, or discoid lupus/lichen planus overlap. Many of these lesions also require a biopsy for diagnosis so if you feel that a patient has lupus, ask the dermatologist to biopsy the lesion rather than treating it empirically with topical steroids
- Oral ulcers - buccal, tongue or nasal
- Non-scarring alopecia
- Synovitis - two or more joints or tenderness of 2 or more joints and 30 minutes or more of AM stiffness

SLICC Clinical Criteria (cont)

- Renal abnormalities - 500mg of protein or more in 24 hour urine or red blood cell casts
- Neurologic abnormalities - seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy or acute confusional state (delusional state)
- Hemolytic anemia
- Leukopenia of less than 4000/mm3 cells or lymphopenia of less than 1000 cells/mm3 at least once
- Thrombocytopenia with platelets less than 100,000 at least once
SLICC Immunologic Criteria

- Positive ANA above the reference range
- Positive ds-DNA of two times or more above the normal level
- Low serum complements - C3, C4, CH50
- Positive direct Coombs test in the absence of hemolytic anemia
- Anti-phospholipid, lupus anti-coagulant, false positive RPR, medium or high anti-cardiolipin antibodies or anti-beta glycoprotein antibodies

Serologic tests in Lupus

- Only 11-13% of patients with a positive ANA have confirmed lupus
- Sun exposure can cause a positive ANA as can age - 10-37% of adults over the age of 65 have a positive ANA
- In healthy individuals, the ANA can be positive in 3-15%
- Multiple medications can cause a positive ANA without symptoms of lupus

Drug-Induced positive ANAs (so try to avoid these meds in patients with lupus)

- Hydralazine (Apresoline)
- Isoniazid
- Chlorpromazine
- Methyldopa (Aldomet)
- Minocycline
- Anti-convulsants
- Anti-thyroid drugs
- Beta-blockers
- Fluorouracil agents
Drug-induced positive ANAs (cont)

- HCTZ
- Interferon
- Penicillamine
- Statins
- Sulfasalazine
- Calcium channel blockers
- Ace inhibitors
- Ciprofloxacin
- Clonidine

Drug-induced positive ANAs (cont)

- Estrogen and oral contraceptives
- Hydroxyurea
- Lithium
- Penicillin
- Rifampin
- Tetracycline
- Gemfibrozil
- TNF-inhibitors

Serologic tests in lupus (cont)

- A positive SSA/SSB suggest Sjogren’s syndrome and suggests that a patient might be susceptible to neonatal lupus or complete heart block in the fetus developing if she becomes pregnant
- A positive ENA/RNP is specific for mixed connective tissue disease
- A positive anti-centromere antibody can be seen in patients with Raynaud’s, scleroderma, CREST
- A positive Sm is very specific for lupus
- A positive dsDNA is seen with lupus nephritis
- A positive ssDNA or anti-histone antibody is seen in drug-induced lupus
Serologic tests in lupus (cont)

- The symptoms of lupus, fibromyalgia and other connective tissue disease can often overlap.
- Many patients in Dr. Dubois clinic (who is considered by many as the father of lupus) who were initially diagnosed with lupus but based on updated serologic tests were found to have fibromyalgia (FM) rather than SLE.
- Symptoms of lupus that can be seen in FM include Raynaud’s, elevated CPK, generalized arthralgias/myalgias, low titer positive ANA, sun sensitivity.
- The Avise 2.0 assay can be helpful in differentiating lupus from other conditions but is not available at clinical laboratories but only in physician offices.
- It is a composite index of many serologic tests that has been validated to differentiate lupus from other conditions.

Co-morbid conditions in SLE

- Cardiovascular disease (CVD)
  - Increased risk of coronary microvascular disease e.g. myocardial endothelial dysfunction.
  - Two times the risk of CVD as women without SLE.
  - Increased risk of myocarditis and pericarditis.
  - Liebman-Sacks endocarditis-sterile vegetations on the valves.
  - Elevated levels of pro-inflammatory HDL which correlate with early cardiovascular morbidity and mortality.

Co-morbid conditions in SLE (cont)

- Lupus nephritis
  - Proteinuria.
  - Hematuria.
  - Positive ds-DNA antibodies.
  - Low complements.
  - Can cause renal failure.
  - Present in up to 40% of patients with lupus.
  - Increased risk in Hispanics, blacks and women.
  - Associated with increased morbidity and mortality.
Lupus Nephritis (cont)

- Class 1 - minimal mesangial lupus nephritis
- Class 2 - mesangial proliferative lupus nephritis
- Class 3 - focal lupus nephritis (active and chronic; proliferative and sclerosing)
- Class 4 - diffuse lupus nephritis (active and chronic; proliferative and sclerosing; segmental and global)
- Class 5 - Membranous lupus nephritis
- Class 6 - Advanced sclerosis lupus nephritis

Lupus Nephritis (cont)

- Any patient with lupus and an active urinary sediment (WBCs, RBCs, protein) should have a renal biopsy performed to determine if specific treatment for lupus nephritis is necessary
- Even patients without an active urinary sediment can have an abnormal renal biopsy but not severe enough to be treated which is the reason that it is not recommended to perform a renal biopsy in all lupus patients
- The goal of therapy is to normalize renal function or at least prevent progressive loss of renal function

Treatment of SLE

- Goal of treatment is to improve quality of life, reduce morbidity and mortality, reduce dose of steroids and induce remission if possible
- Treatments include steroids, azathioprine, methotrexate, leflunomide, hydroxychloroquine, mycophenylate mofetil, rituximab and belimumab, but only the latter is FDA-approved for treating lupus
Treatment of lupus: hydroxychloroquine

- Michelle Petrie, a lupus expert at Johns Hopkins, recommends that all lupus patients, no matter how mild or severe their disease, take hydroxychloroquine which has been proven to decrease the risk of developing lupus nephritis.
- Hydroxychloroquine is commonly used as mono therapy (perhaps with an NSAID if no renal impairment) for patients with mild lupus with symptoms of pleurisy, arthritis, rash, sun sensitivity, oral ulcers and alopecia.
- Side effects of hydroxychloroquine include sun sensitivity, rash, diarrhea, flatulence, alopecia, increased skin pigmentation, headaches, light-headedness and retinal toxicity that can result in blindness.

Aminoquinolones

- Retinal
  - Arteriolar narrowing
  - Vascular sheathing
  - Peripheral and macular pigmentary changes
  - Bullseye pigmentary maculopathy
  - Continues to progress after cessation, secondary to accumulation in pigmentary tissue; improves only if stopped very early.

Plan and Prognosis

- Patient stopping plaquenil immediately
- Risk of deterioration could continue for 6 years due to long half-life of drug.
**Classic Criteria for Screening**

**Subjective**

- BASELINE exam and then
- Q 6 months
  - Color plates-H-R-R (sens 76.7%; spec 88%) superior to Ishihara (sens 43.3%; spec 96% Vu et al) : mild B-Y proton R-G
  - Red 10-2 visual fields
  - High resolution exam of macula
  - Macular dazzle

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**2010 AAO Objective Screening Guidelines**

**Baseline: at Initiation of Treatment**

- Thorough ocular examination documenting any preexisting conditions (color funds photos useful for documentation)
- Humphrey visual field central 10-2 white-on-white pattern
- At least one of the following objective tests, if available:
  - Fundus autofluorescence (FAF)
  - Multifocal electroretinogram (mfERG) (can replace visual fields)
  - Spectral domain OCT (SD-OCT)

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**Ongoing Monitoring**

- Annual ophthalmic examination
- Ancillary testing is not necessary within first 5 years unless abnormalities are noted on baseline examination
- Earlier and more frequent screening for those at higher risk for toxicity
- After five years of treatment:
  - Annular ocular examination
  - 10-2 threshold field testing
  - One of the objective tests
  - SD-OCT: subtle parafoveal abnormalities
Treatment of Lupus: prednisone

- For mild lupus, try to avoid steroids if possible due to multiple steroid side effects including diabetes, osteoporosis, glaucoma, cataracts, obesity, fluid retention, increased risk of infection, delayed healing
- For life-threatening lupus e.g. CNS, lupus nephritis, begin 1000mg IV for 3-5 days
- For moderate lupus eg pleural effusions, skin ulcerations, generalized alopecia goal is to taper off steroids but if not possible maintain dose at 5-10mg of prednisone daily

Treatment of lupus: azathioprine

- An immunosuppressive antimetabolite used to prevent rejection of renal transplants and used off-label to treat lupus
- It is a purine analogue that interferes with DNA synthesis and inhibits proliferation of rapidly growing cells
- Used to treat lupus in patients with CNS or renal disease when remission has been induced with other agents
- Usual dose is 1-3 mg/kg for 6-9 months followed by 50-100mg daily
- Adverse reactions include bone marrow toxicity, abnormal liver function tests, increased risk of infection, temporary decrease in spermatogenesis, pregnancy category D, increased incidence of NMSC, PML and lymphoma

Treatment of lupus: azathioprine (cont)

- Laboratory monitoring: CBC weekly during the first 4 weeks, then every 2 weeks during month 2 and 3 then monthly
- It is recommended to consider either genotype or phenotype testing for TPMT (thioprine methyltransferase) to determine if patients are at increased risk of toxicity
- Approximately 11% of the population has reduced TPMT activity and 0.3% of the population have true deficiency of TPMT
- In these patients, active 6-MP accumulates increasing the risk of bone marrow toxicity
- If treatment is necessary, it is recommended to use a lower dose
Treatment of Lupus:
mycophenolate mofetil (MMF)

- An immunosuppressant drug approved to prevent rejection in organ transplantation and is used off-label to treat lupus including lupus nephritis (data reviewed later)
- It is also used as a steroid sparing agent for other types of lupus
- It is an oral agent with usual doses of 500-1500mg BID
- Side effects include fetal deformities, increased risk of lymphomas and NMSC, increased risk of infection, nausea, rash and bone marrow toxicity

Treatment of lupus:
Methotrexate

- Methotrexate is used off-label to treat the arthritis associated with lupus and as a steroid-sparing agent
- It can cause pulmonary toxicity including pneumonitis, interstitial infiltrates and pulmonary fibrosis and therefore should not be used in lupus patients who have pulmonary involvement so it is recommended to get a baseline CXR
- Other toxicities include bone marrow suppression, alopecia, nausea, headache, sun sensitivity (which is already present with lupus), increased risk of infection, delayed healing, hepatotoxicity and increased risk of lymphoma

Treatment of Lupus:
Methotrexate (cont)

- Pregnancy category X as can cause fetal death or teratogenic effects when administered to a pregnant woman.
- Pregnancy should be avoided if either partner is receiving methotrexate, during and for a minimum of 3 months after therapy for male patients and during and for at least one ovulatory cycle in female patients
- Monitoring for toxicity includes a baseline CBC, liver function tests, renal function and then every 4-8 weeks thereafter.
- Some guidelines recommend a baseline hepatitis B and C screen
Treatment of Lupus: Leflunomide

- Leflunomide is a pyrimidine synthesis inhibitor which is approved for treating RA but is used off-label to treat lupus as a steroid-sparing agent.
- It shares all of methotrexate toxicities except for pulmonary adverse events and monitoring for adverse events is similar.
- It is pregnancy category X.
- Upon discontinuing leflunomide, women who wish to become pregnant must take cholestyramine 8 grams 3 times a day for 11 days to eliminate the drug from the body.

Treatment of Lupus: NSAIDs

- Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat the arthritis associated with lupus.
- NSAIDs increase the risk of GI perforations, ulcerations and bleeds, increase cardiovascular morbidity and mortality and can cause acute tubular necrosis and chronic kidney disease.
- If a lupus patient has any of these pre-existing conditions, NSAIDs should be avoided.

Treatment of Lupus: Belimumab

- An anti-B lymphocyte stimulator (BLyS) monoclonal antibody given intravenously once monthly.
- Reduces the number of B cells and serum IgM levels over time.
- Approved for treating active lupus with positive antibodies despite standard treatment but is not approved for treating lupus nephritis or CNS lupus.
- It has not been studied in combination with cyclophosphamide or other biologics but compared to standard therapy improved overall clinical outcomes.
- Live vaccines cannot be given while on therapy or 30 days before therapy.
Treatment of lupus:
Belimumab (cont)
- Is the first medication approved for treating lupus in 50 years
- Side effects include increased risk of infection, depression, chest pain, SOB, nausea, dizziness
- Is pregnancy category C
- Women need to use adequate contraception during use and for 4 months after
- Dosing is 10mg/kg at 2 week intervals for the first 3 doses followed by one dose every 4 weeks
- In clinical trials it was shown to allow reduction in the dose of prednisone

Treatment of Lupus:
Rituximab
- Rituximab is a B-cell depleting therapy that is approved for treating rheumatoid arthritis and lymphoma
- It has been used off-label by rheumatologists for many years prior to the approval of belimumab as no new therapies had been available for decades
- However, a recent randomized, double blind placebo-controlled phase 2/3 clinical trial demonstrated no difference between placebo and rituximab in the entire population of subjects but in the Hispanic and African American subset, there was a clinical benefit

Treatment of Lupus:
Cyclophosphamide
- Used prior to the approval of MMF to treat lupus nephritis
- Is associated with decreased fertility, increased risk of infection, increased risk of malignancy especially bladder cancer, nausea and vomiting, bone marrow suppression, alopecia and hemorrhagic cystitis (concomitant administration of mesna, a thiosulfate that binds the offending agent, acrolein, can reduce this toxicity
- Consideration might be given to freezing eggs in women who have not completed their child bearing
- Currently, is considered as second line therapy to MMF
Treatment of Lupus Nephritis

- The American College of Rheumatology published guidelines in 2012 regarding screening, treatment, and management of patients with lupus nephritis.
- All lupus nephritis patients with proteinuria greater than 0.5 gm/day should be treated with an ACE inhibitor or an ARB as these medications reduce proteinuria by about 30% and delay the progression of chronic renal disease.
- All lupus nephritis patients should be treated to control hypertension with a target of 130/80 or less to delay progression of renal disease.
- Statin therapy should be given to lupus nephritis patients with a LDL of greater than 100mg/dl as a GFR of less than 60 is a risk factor for accelerated atherosclerosis.

Treatment of Lupus Nephritis (cont)

- Lupus nephritis patients with Class I or II lupus nephritis generally do not require immunosuppressive therapy.
- In general, patients with class III and IV lupus nephritis need treatment with glucocorticoids and immunosuppressive agents.
- For these patients, 3 grams of MMF for 6 months followed by maintenance therapy for 3 years or IV Cytoxan 500-1000mg/m2 monthly for 6 months plus GC IV pulse followed by prednisone 0.5-1.0 mg/kg/day.

Treatment of Lupus Nephritis (cont)

- Once induction therapy is completed either azathioprine 2mg/kg/day or MMF 2gm/day should be used as maintenance therapy.
- If patients fail to improve by 6 months, the alternative therapy should be used with IV pulse steroids.
- If a lupus nephritis patient is pregnant, steroids plus azathioprine should be used even though the latter is pregnancy category D as cross-sectional studies have shown that the risk of fetal abnormalities are low.
Summary

- Lupus is a serious autoimmune disease that affects primarily young women
- A positive ANA alone does not make a diagnosis of lupus
- Early diagnosis and treatment is imperative in an attempt to prevent worsening of disease including progression to renal failure
- Once a patient has been diagnosed with lupus, consultation with a rheumatologist or nephrologist (for those patients with lupus nephritis) should be considered to establish a course of treatment
- Newer treatments are greatly needed in an attempt to control disease activity without significant toxicity

Bibliography

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