Systemic Lupus Erythematosus and Antiphospholipid Syndrome

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SLE: Still a Mystery after Centuries

- As early was 400 B.C, Hippocrates described what was thought to be the first case of lupus.
- 1850 the term systemic lupus was used to describe the symptoms of lupus.
- Lupus is derived from the Latin word for WOLF. Referring to the disfiguring facial rash of lupus patients.
- Lupus is known as the great imposter since it can affect any organ.
- Lupus can affect the lungs, heart, blood cells, joints, kidneys, liver, eyes, central nervous system, and the skin.

Autoimmune Disorder-SLE

- SLE is a chronic multisystem autoimmune disorder that can affect every major organ system.
- SLE causes inflammation, tissue injury, organ damage, and ultimately organ dysfunction or failure.
- Your immune system has a primary job and that is to protect you and help the body heal. In SLE the immune system which is in overdrive begins to attack your own tissues. The exact cause of this misdirection is still not known.
- One defect that is known is a process called apoptosis (programmed cell death). In SLE, cellular antigens exposed during cell death incite an immune response.

Onset of symptoms until diagnosis.

- Depending on presenting symptoms, it can take up to 5 years before recognizing it as SLE. Most frustrating.
- 30-50% of SLE patients have organ damage within the first 5 years.
- SLE disease activity can be active in the absence of symptoms thus the need for monitoring and blood studies.
- It is estimated that 75% of SLE patients have persistently active disease. Not all SLE patients with SLE are symptomatic.
- Important to have lab studies for SLE and be monitored regularly.
- 5- year Survival Rate in 1960 was 50% and now is 95%.

Predisposing Factors for SLE

Genetic factors do play a role in SLE. In twins they found a 66% susceptibility. Only 2% of children whose mothers have lupus will likely develop lupus. SLE is not directly inherited.

Gender: Women to men ratio 9:1. Asian and African-American, Native Americans ratio 1:250 vs 1:1000 in Caucasian women.

Higher occurrence in low-income areas.

Environmental factors such as sun exposure, trauma, cigarette smoke, air pollution, pesticides, silica dust.

Drug exposure such as sulfa, quinidine, minocycline, hormonal therapy and estrogens. BCP with estrogen base not recommended.

Hallmark of SLE

- Hallmark or systemic lupus is abnormal antibody production.
- This is a B cell activity primarily.
- Specifically, the anti-DNAds antibody and the anti-Smith antibody (anti-SM antibody) are associated with SLE.
- 97% of patients with SLE will have a positive ANA in a titer of 1:80 or greater. This titer can change over time. Can have a high titer and not severe disease or a low titer and have serious disease. This is where knowing the clinical disease and if major organs are involved makes a significant difference in clinical diagnosis.

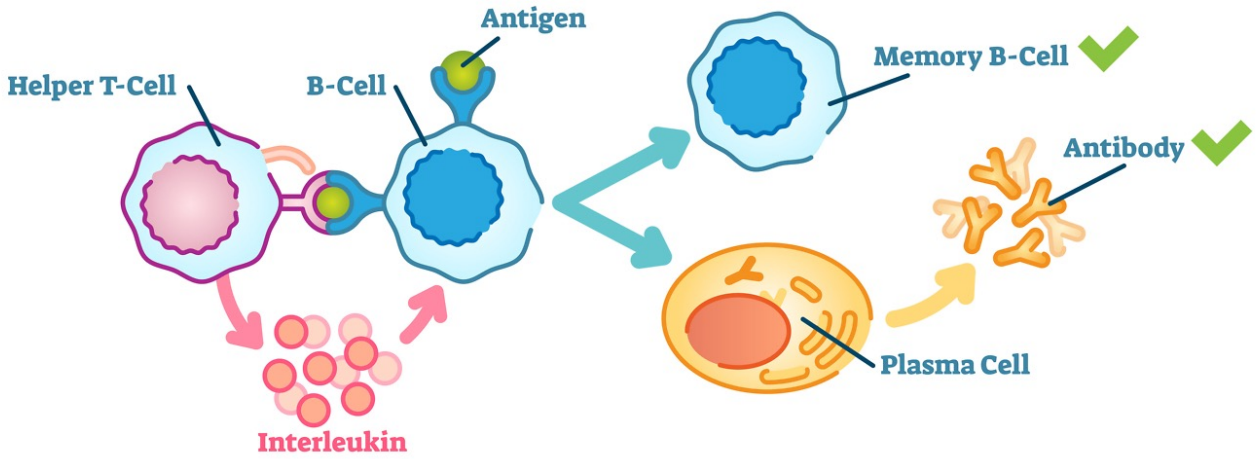
Immune disorder and cell activity

The bone marrow produces white blood cells that go into the blood stream. Lymphocytes are one of the types of white blood cells.

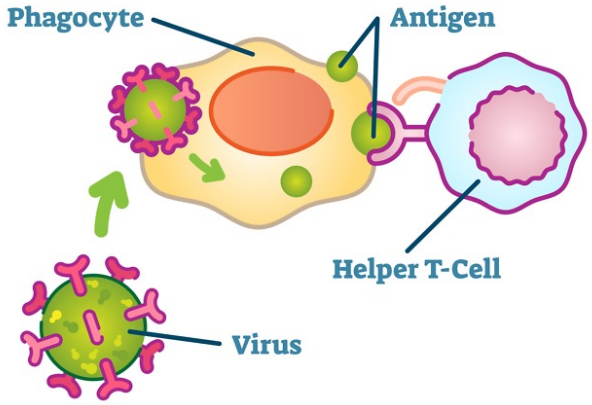
The function of lymphocytes are critical to our survival. Lymphocytes are T and B cells. T cells develop from stem cells in the bone marrow. They protect the body from infection and help fight cancer. T cells protect by destroying infected cells or cancerous cells. They help the B – lymphocyte. One type of T cells are known as helper cells. Another type of T cells are known as killer cells.

B cells or B lymphocytes produce antibodies to protect us, can interact with the T cells, secret inflammatory cytokines and, as in lupus, make antibodies against your own cells.

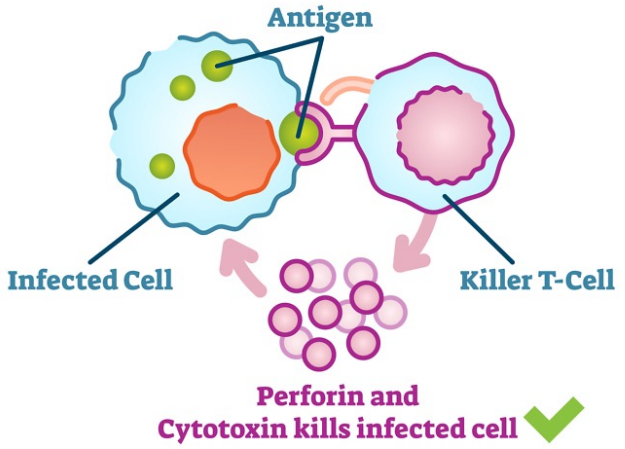
B-Cells and T-Cells



T-cell Activation



Killing of Infected Cell



Criteria for Systemic Lupus

ACR criteria for systemic lupus are the following. 4 out of the 11 are needed to establish the diagnosis of lupus.

Malar rash

Discoid rash

Photosensitivity

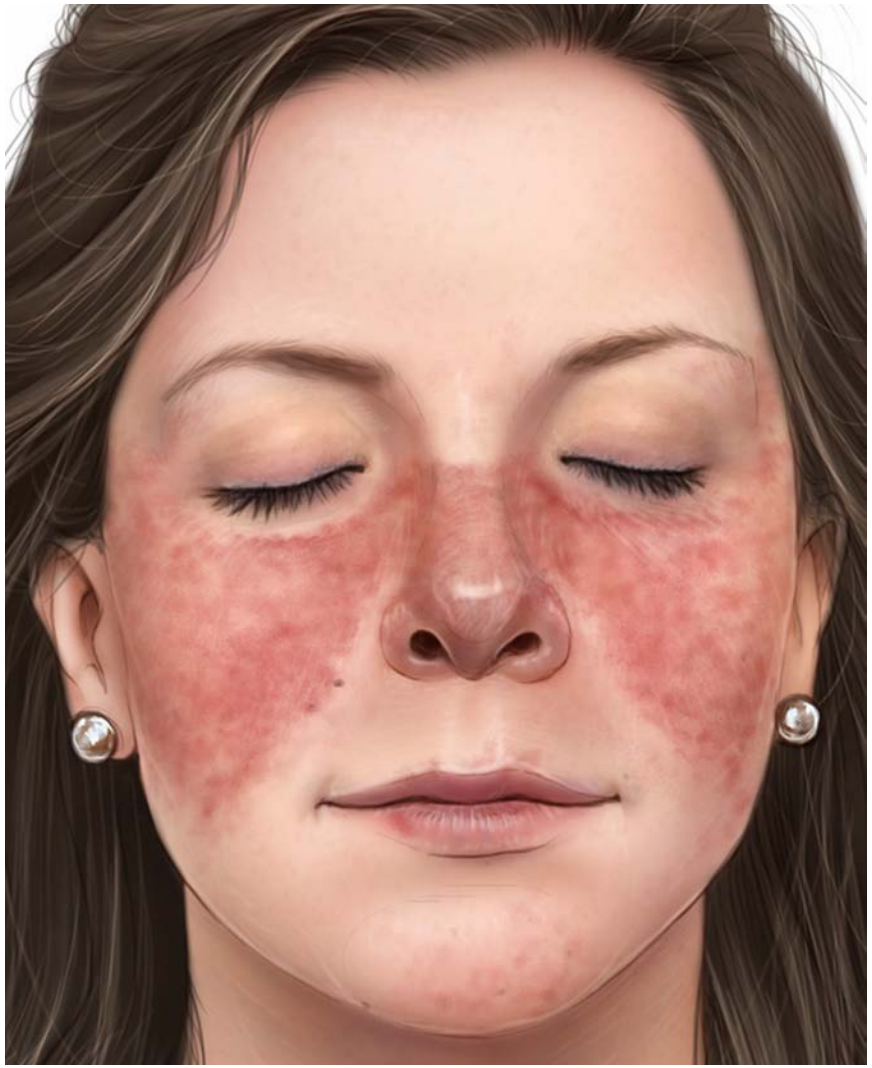
Alopecia

Raynaud’s phenomenon

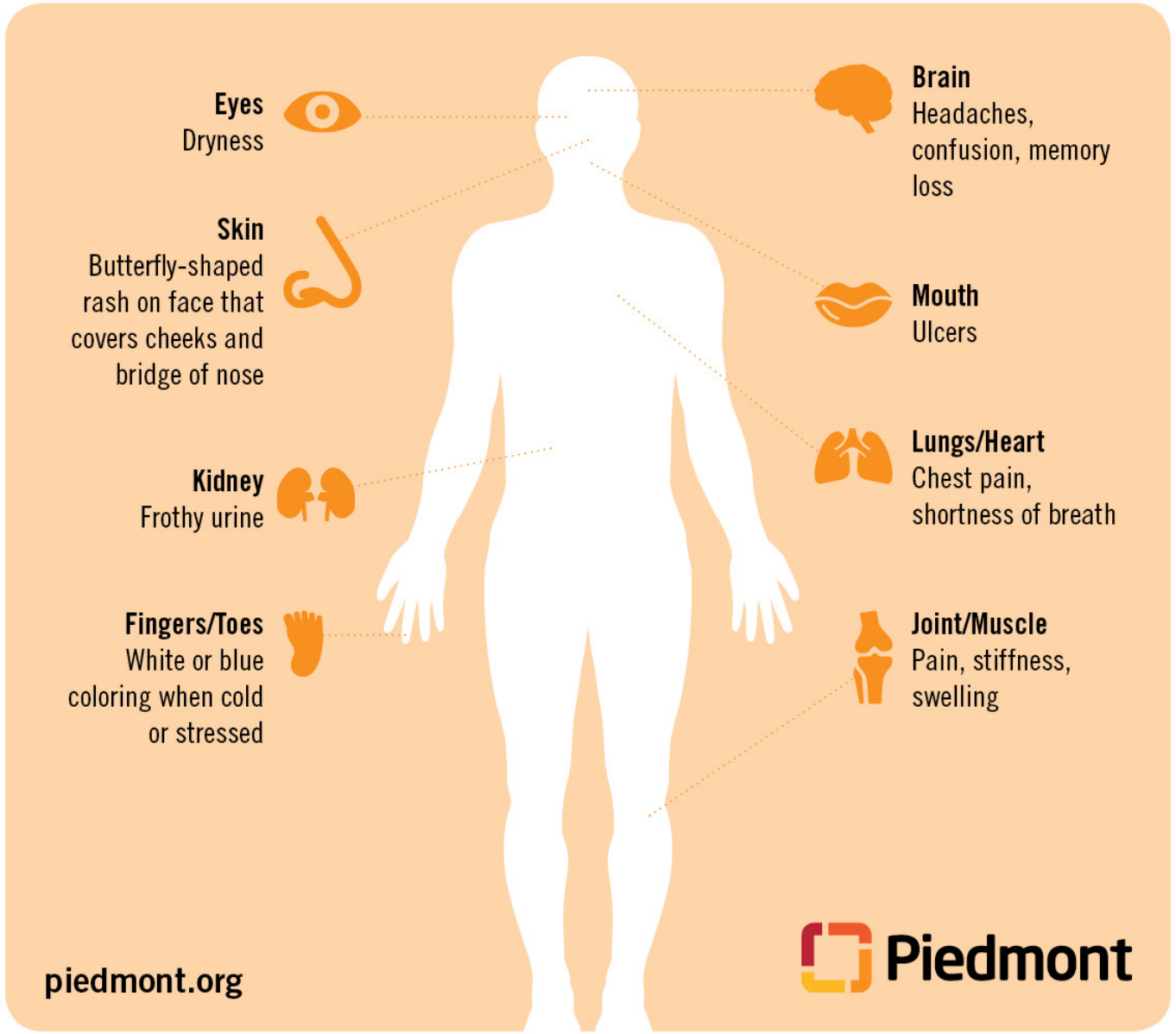
Oral / Nasal Ulcers

Criteria for systemic lupus

- Arthritis (non-erosive arthritis involving 2 or more peripheral joints.
- Serositis (pleurisy or pericarditis, abdominal serositis)
- Renal disease (proteinuria greater than 500mg daily or cellular RBC or casts in urine)/lupus nephritis.
- Neurologic disorder (Headaches, seizures, psychosis)
- Hematologic disorder (low white blood count, low hemoglobin, low platelet counts.
- 4 of these criteria present can offer 95% specificity and 85% sensitivity for SLE.

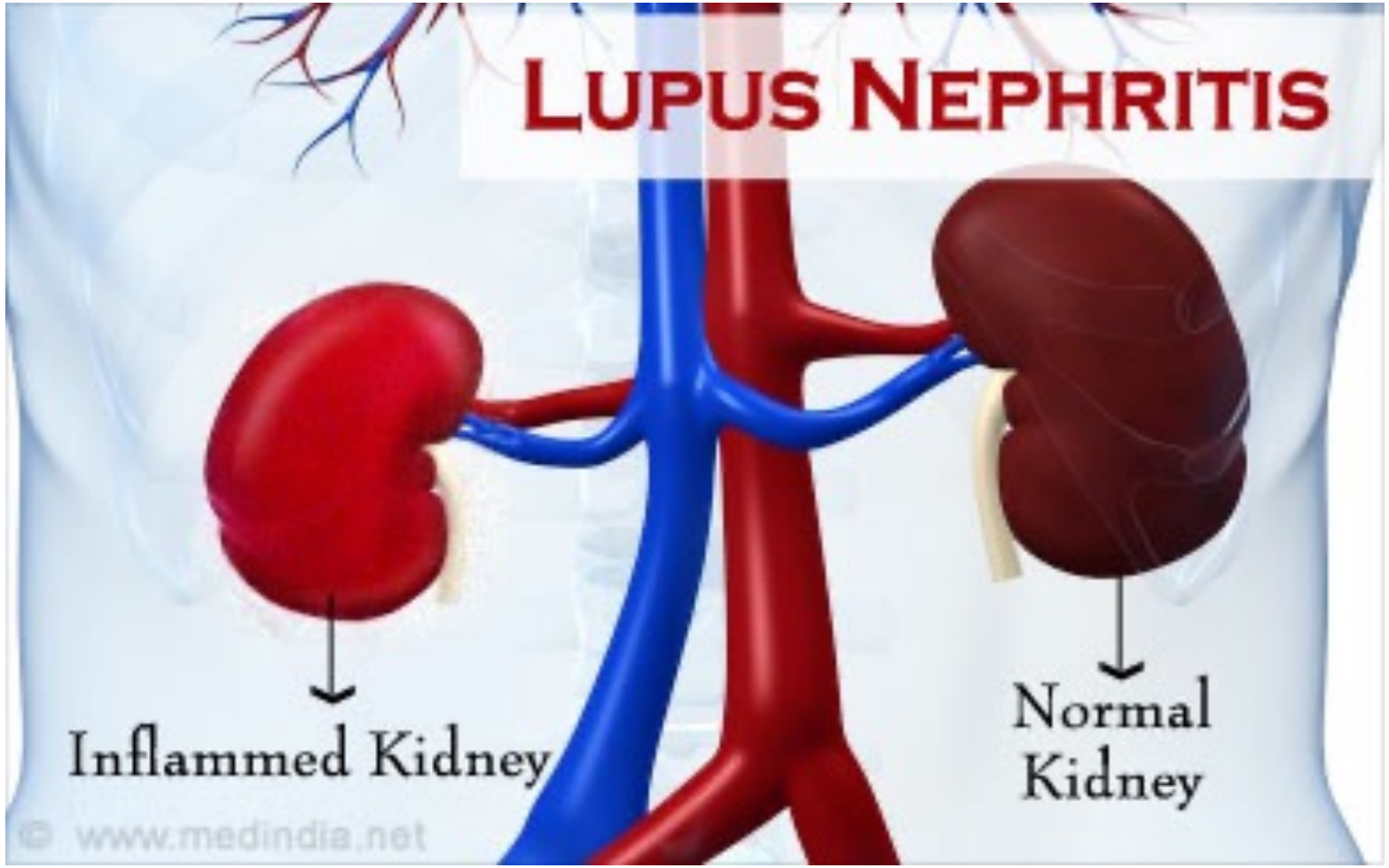


Common Lupus Symptoms



Cardiovascular Disease in SLE Population

- Leading cause of SLE morbidity and mortality.
- Overall risk of CV events in SLE patients is 2.66 times higher than the normal population. Risk factors are age, hypertension, hyperlipidemia, obesity, and Prednisone.
- Recent studies emphasize the steroid dosage, presence of anti-DNA ds, and lupus anti-coagulant positivity as high-risk factors.
- Hydroxychloroquine (Plaquenil) use decreases the risk of C.V risk
- What can you do to lessen this risk? Take your medication, exercise, diet, control blood pressure, etc. All the things you would do to lessen heart disease if you did not have lupus.


LUPUS NEPHRITIS
Inflammed Kidney
Normal Kidney
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Lupus Nephritis

- Kidney involvement: Occurs in 50% of people with lupus.
- Proteinuria, elevated BUN, decreased creatinine clearance, and elevated serum creatine are signs of renal involvement.
- Renal biopsy may be needed for degree of disease activity.
- Multi-target therapy should be routine.
- Steroids, MMF(mycophenolate), Cytoxan, Imuran, and Rituxan.
- Adjunct therapy including ACE inhibitors and angiotensin receptor blockers as well as Hydroxychloroquine are often needed for control of the blood pressure and inflammation.
- Patients on MMF(Cell-Cept/ brand name) plus Hydroxychloroquine for membranous nephritis . 64% achieved remission in one year vs. 22% of those on Cell-Cept alone.

Neuropathy in SLE

- Peripheral neuropathy is seen in 30% of SLE patients who have EMG studies. EMG is electromyography.
- Small fiber neuropathy can be missed since it does not show up on an EMG.
- Must have a skin biopsy for diagnosis. Immunostaining is done to detect intraepidermal nerve fibers.
- Small fiber neuropathy is now recognized as a common cause of peripheral neuropathy. Symptoms are pins and needles, pricks, tingling, numbness, burning pain, or electric shock-like-sensations that are brief.

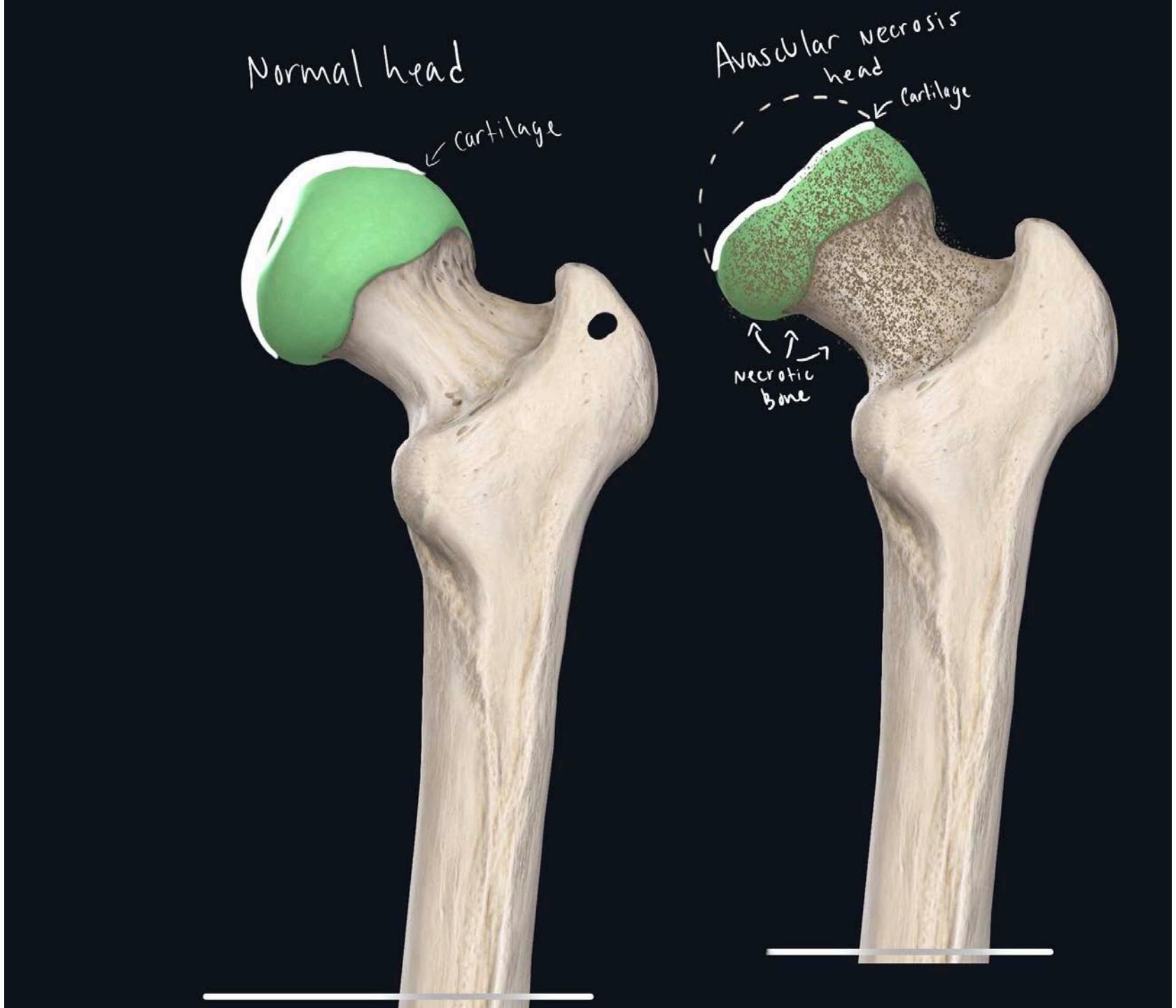
Musculoskeletal Manifestations

- 90% of SLE patients at some point have joint inflammation and pain. It is non-deforming unlike rheumatoid arthritis. Treat with NSAID (avoiding the most toxic to GI tract). Cover with cytoprotective therapy.
- Treat inflammatory arthritis with Hydroxychloroquine. Safe.
- 1% can develop retinal toxicity. New equipment to detect early signs of toxicity of Hydroxychloroquine is available. Yearly monitoring after the first 5 years of therapy.
- Reduce the dosage of Hydroxychloroquine if there is renal insufficiency.


INFLAMMATION

Musculoskeletal Complications

- Osteonecrosis: 14% of patients in a large study showed bone necrosis (bone death) primarily in the hips. This is felt to be due to the steroids used to treat the disease. MRI is best to detect the osteonecrosis. Treatment is with a core decompression in the early stages.
- AVN (avascular necrosis) can be associated with trauma, dislocation, steroids, and alcohol. The etiology of the process is still not well understood.
- Osteoporosis (loss of bone mass) can be seen in 64% of patients with SLE. Related to highest dose and cumulative dose of Prednisone, Vit. D deficiency, and proton pump inhibitors.


Normal head
Cartilage
Avascular Necrosis
head
Cartilage
Necrotic
Bone

Some insights into Management of SLE

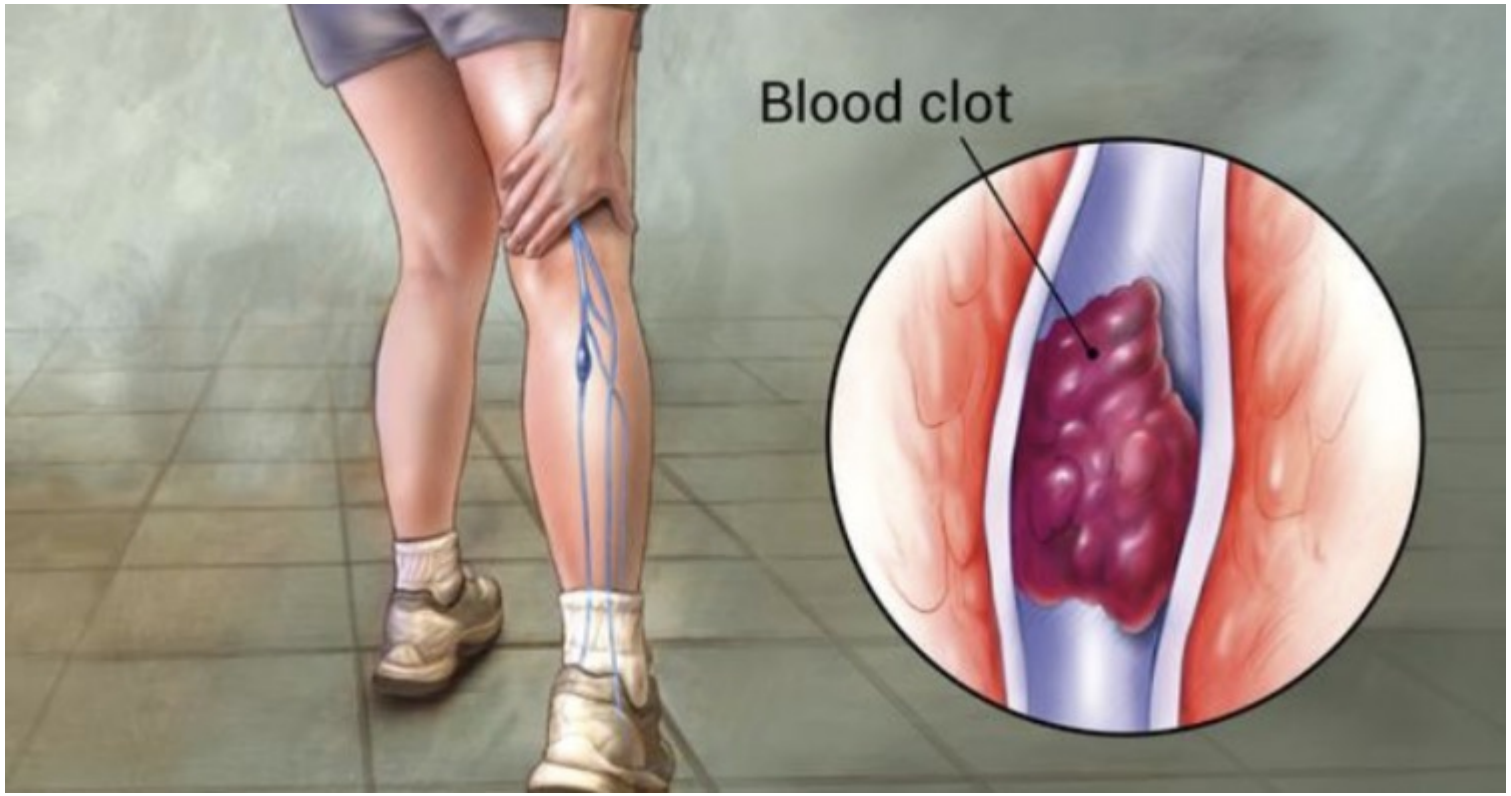
- Type of lupus (systemic lupus, cutaneous lupus, drug induced lupus, and neonatal lupus). Degree of organ damage, acute or chronic stage. This discussion pertains to systemic lupus.
- Hydroxychloroquine, NAID, Steroid creams for skin involvement or injections, and systemic steroids for more serious disease states.
- Why steroids. They WORK and they Work quickly for the most part.
- High dose steroids has recently been redefined by John Hopkins Cohort as greater than 6 mg a day. High dose steroids increases later organ damage significantly.
- Multi drug approach is often taken with serious and life-threatening disease. Frequently used drugs are Hydroxychloroquine, Methotrexate, Imuran, Cytoxan, Mycophenolate (Cell-cept), Benlysta, Steroids, NSAID. This is not a complete list.

Benlysta: First New Drug in 50 Years for SLE

- In 2011 the first specific drug in 50 years was approved for SLE. It is a human monoclonal antibody, a protein, that specifically recognizes and blocks the histologic activity of the B lymphocytes stimulator BLYS (bliss). A naturally occurring protein that prolongs the survival of B cells. These B cells produce antibodies that target your own cells.
- This drug is specific for lupus and no other diseases. It targets specific immune cells.
- Approved only for active antibody positive lupus receiving standard therapy. Not evaluated in severe nephritis, or CNS lupus, or used in combination with Cytoxan.

Antiphospholipid Syndrome

- Rare disease entity. 10% of SLE patients have APS.
- APS Syndrome is a condition where the immune system mistakenly creates antibodies that attack tissues in the body having to do with the cell membranes made of phospholipids.
- These antibodies can cause blood clots to form in arteries and veins.
- Blood clots can form in the legs, brain, kidneys, spleen, etc. Can lead to heart attacks and strokes.
- During pregnancy this can result in miscarriages and stillbirths.


Blood clot

Signs and Symptoms of APS Syndrome

- Blood clot formation in the legs or DVTs.
- Repeated miscarriages or stillbirths.
- Stokes or CVAs in young people or people with no known risk factors for cardiovascular disease.
- TIAs or transient ischemic attacks which last only a few minutes. No permanent damage is done.
- Livedo reticularis, which is rare , the blood vessels near the surface looks lacelike.
- Neurologic symptoms: headaches, migraines, seizures, dementia.
- Low platelet count: bleeding from gums, nose, etc.

APS is autoimmune in origin

- Antibodies associated with APS: antiphospholipid antibody, lupus anticoagulant, anti-cardiolipid antibody, and anti-Beta2glycoprotein-1antibody.
- Antibody testing should be done if the APS Syndrome is suspected. Has to be two positive tests 12 weeks apart. The first done after the initial event followed by the retest in 12 weeks.
- A person can have positive APL antibodies without the active syndrome. These can be brought on by infections(bacterial, viral, and parasitic). Meds such as oral contraceptives, quinine, amoxicillin, phenothiazines.

Treatment of the APS Syndrome

- Treatment depends on whether one has a low risk profile or a high risk profile. This is formed on the basis of history, physical, and antibody positivity in the blood work.
- Treatment is low dose aspirin.
- Treatment is anticoagulant therapy such as Heparin.
- There is no cure but treatment can prevent the disasters that can occur with this syndrome including miscarriages.