



RhAPP

RHEUMATOLOGY ADVANCED
PRACTICE PROVIDERS

Inaugural National Conference

December 3 – 5, 2020

VIRTUAL CONFERENCE



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PRACTICE PROVIDERS

Rheumatology Labs RHAPP Maiden Voyage

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Faculty Disclosures

Jackie Fritz, RN, MSN, RN-BC

- Research Support: Genentech
- Speakers Bureau: Abbvie, Sanofi Genzyme, Horizon, Amgen

My First Day on the Job

Everything in Nursing is named after some Doctor:

- Swan and Ganz: pulmonary Catheter
- Mobitz: heart Block
- Somogyi: rebound blood sugar
- Wolf Parkinson White: pre- excitation
- Kawasaki: Motorcycle: wait it had a Syndrome attached?
- Wegeners: Bad German Or shorten to help you Understand Granulomatosis with Polyangiitis: GPA? (Much better)
- So SSA and SSB: must have been some labs test for Supercalifragilisticexpialidocious

Let's Start With the Basics

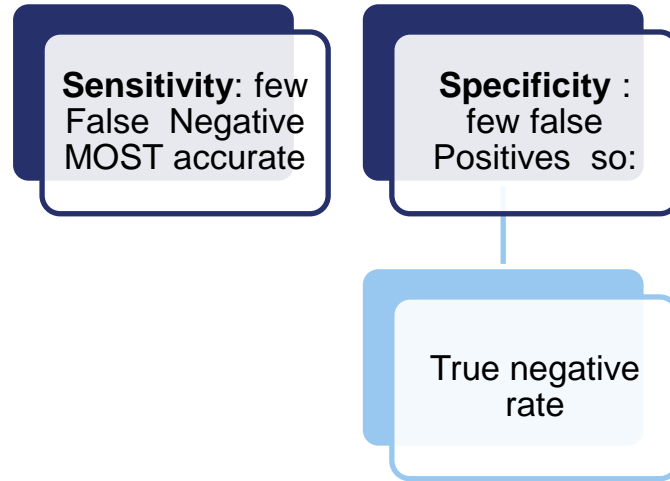
- Understand the principles of a lab test
- Preview of the Test
 - Is it appropriate for the patient?
 - Does it guide our diagnosis?
 - What does the test measure
 - What are the limitations

Telemedicine: Google DUO Gotta Ask Right??

- C/O am stiffness: fatigue, occasional fever
- Muscle pain vs muscle weakness
- Joint swelling
- Alopecia
- Dry Eyes, Dry Mouth
- CP, SOB
- Brain fog
- Restorative sleep
- Can you do a joint count or TP via telemedicine???

Sensitivity VS Specificity

So Before We Start Looking at LAB TESTs



Basics We Learned in School

- IgA: 1st defense in mucous membrane, respiratory and GI
- IgG: protects against bacterial infection humoral response eradicates infection sustained
- IgM: blood, lymph antibody innervated
- IgE: mast cell mediated allergic response

ESR Erythrocyte Sedimentation Rate

- Measures Acute Phase reactant
 - Fibrinogen most common
 - Produced by the liver as a part of an inflammatory response: under control of cytokines Il6, IL1 and TNFa
 - RBC are the messengers of the fibrinogen levels
 - Fibrinogen interacts with RBC to make the sediment fall more quickly
 - Acute phase reactant (CRP) more sensitive

Deviations of ESR

- Women have higher ESR and men
- ESR rise with age
- ESR above 40 mm/h may be associated w:
 - PMR, RA
- Very non-specific
 - Elevated:
 - Infections
 - Malignancy
 - Anemia
 - And some cholesterol lowering agents
 - Does not rise with anemia

CRP Capsular Reactive Protein

- Used to help define acute phase reactivity
- Combined with ESR: called acute phase reactants
- Used as a measure of how well disease is being managed
- Also can be responsive to many other things than just inflammatory processes



Rheumatoid Factor and RA

Prevalence increases and disease duration

- 30 – 50% positive at disease onset
- 75%+ after one year
- 80% after 18 months
- Prognostic Significance
 - PRESENT 1-5% POPULATION
 - INCREASE W AGE > 65 10%
 - HARDLY EXCLUSIVE TO RA

Rheumatoid Factor but NOT RA

- Collagen Vascular diseases
 - Sjogren's Syndrome
 - SLE
 - Cryoglobulinemia
 - Scleroderma
 - Poly/Dermatomyositis
 - **NOT ALL RF+ is Rheumatoid Arthritis**

RF + Non-Rheumatic Diseases

- Chronic Infections:
 - Elicit Chronic immune response
 - Hep C
 - Endocarditis
 - Osteomyelitis
 - Syphilis
 - Cirrhosis
 - Sarcoidosis

Rheumatoid Arthritis

- Anti-CCP: Anticyclic citrullinated peptide
- Above 20 units is +
- Higher CCP the more active the disease
- 97% specific
- Will remain + despite remission
- Eta 14.3.3: good for early RA diagnosis

Anti-CCP Anti-Bodies and RA

- 70-80% Sensitivity
- 90-95% Specificity
- Will remain + even if in remission
- Not used to monitor disease activity
- Diagnosis by ACR criteria
 - 936 patients with early inflammatory arthritis
 - 205 by ACR Criteria
 - 318 Undifferentiated RA
 - 413 Other Diagnoses

Case Study

- 45 year old female with history of tick bite. Joint swelling especially MCP and PIP. Responds well to steroids given in shorts courses. All Lyme tests are negative. CCP and ETA 14.3.3 also negative. ESR and CRP are quite elevated.
- Parvo virus positive????
- The Tick bit the dog (which had Parvo) and then the patient!
- **Diagnosis:** Reactive RA

Lots to Learn...At Least for Me

Let's Start With Basics of ANA

- ANA how referral do you get weekly for + ANA and the poor patient fearful has already been diagnosed with SLE!
- Females: 17.8% +
- Males: 9.6 + peaking both around age forty
- ANA: as you know stands for Antinuclear Antibody which **can** mean that you are allergic to yourself! ...or not
- Popular well “researched” books: invite you to avoid allergy food, gluten, nuts, Lactose and oh yes drink a bottle Guaifenesin daily!

Let's Talk Before We Go Further

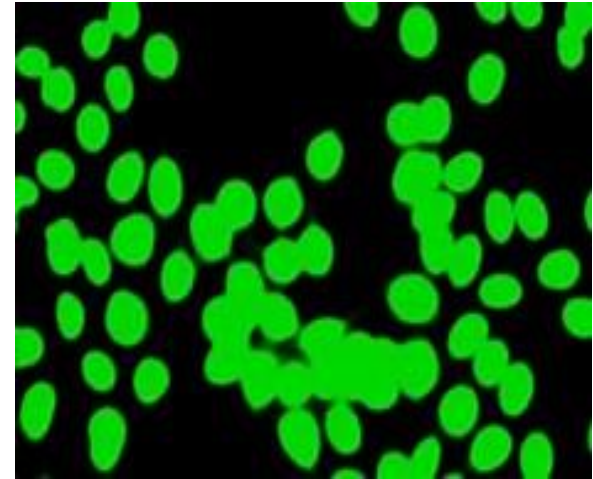
- ANA is not nearly as specific for SLE as it is sensitive:
 - Autoimmune Thyroid disease
 - Other Vascular Collagen Vascular Disease (90% SSC)
 - Viral Infections
 - Malignancies
 - Normal people with low titers (ratio 1:80)

ANA Specificity

- ANA
 - Active SLE 95%
 - MCTD 95%
 - Diffuse SSC 70-90%
 - Systemic Sclerosis
 - CREST: C = Calcinosis, R = Raynauds, E= Esophageal mobility, S = Sclerodactyly, T= Telangiectasia
 - Primary Sjogren's > 20%
 - RA 40-50%
 - Drug induced SLE 100%

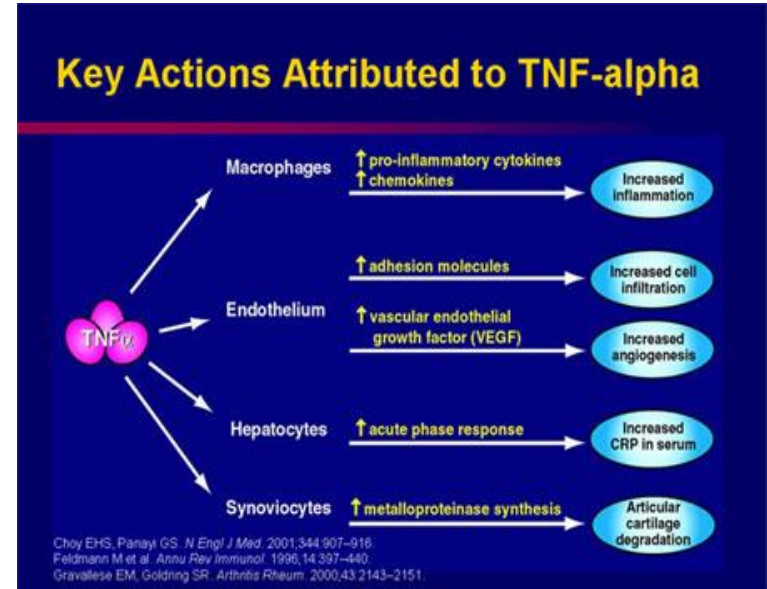
ANA Patterns: Homogeneous

- **Homogenous:** very specific to SLE, confirm with:
 - ANTI ds DNA
 - 50-60% sensitive for SLE
 - 90-95% specific
 - + = correlates with more renal and systemic disease
 - Possible implication to glomerulonephritis



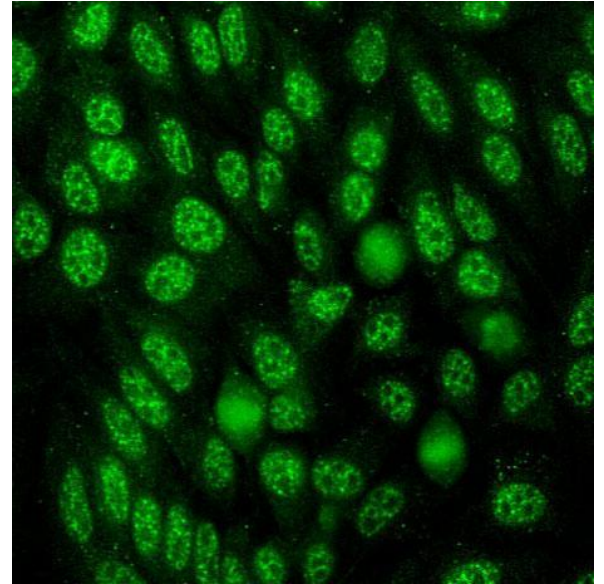
ANTI_{ds} DNA Specificity

- Active SLE 60%
- Can be implicated in SLE Nephritis
- 90% TNF_α AB Induced SLE
- Consider anti-histone
- Chimeric: means Mouse protein (mab large molecule)
- More Cheese?



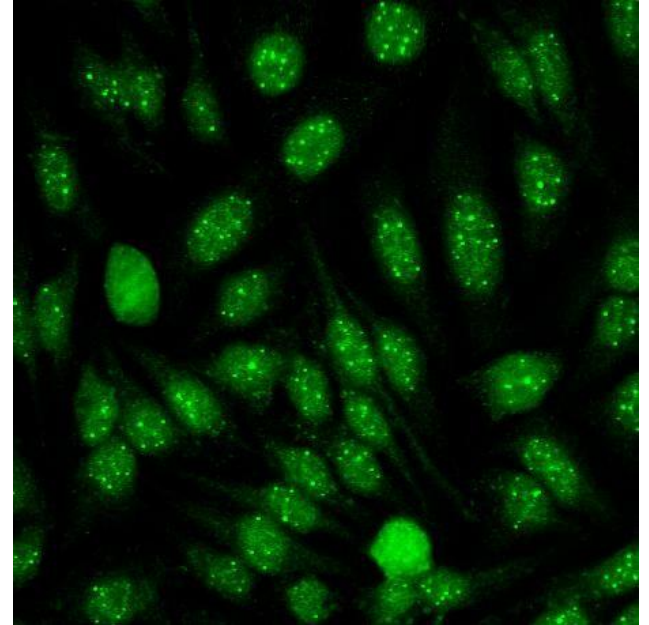
Speckled Patterns ANA

- Anti-SSA (RO)
- Anti-SSB (LA) both SLE and Sjogren's
- Anti-SCL 70 (SSC)
 - Anti-Smith (SLE)
 - Anti-RNP (MCTD)



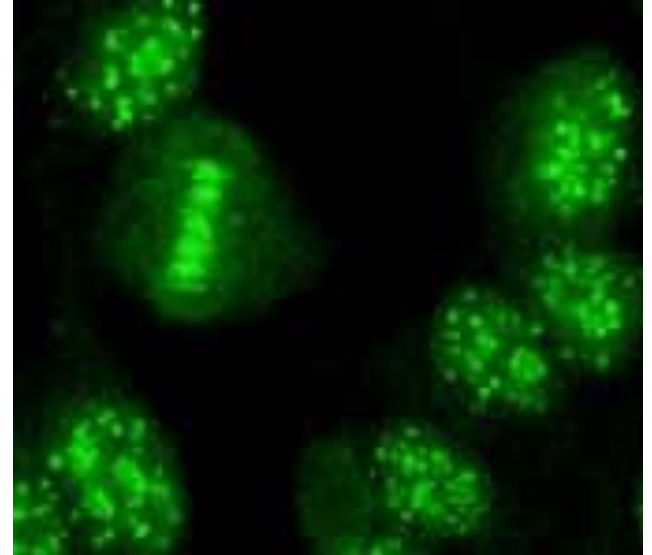
ANA Patterns: Nucleolar

- 90% sensitive to Systemic Sclerosis
- Scleroderma
- SCL 70
 - 25 % Sensitive
 - 90% Specificity
 - Risk for more systemic organ involvement



ANA Patterns: Anti-Centromere

- Looks like Spindle
- Limited “CREST” 60-80%
- Diagnostic/prognostic significance
 - Isolated Raynauds 25%
 - Pulmonary HTN
 - Progressive Systemic Sclerosis



ANA Patterns

Staining	Antigen	Disease
Diffuse or homogeneous	Deoxyribonucleoprotein, histone, ds DNA	Systemic lupus erythematosus (SLE)
Peripheral or rim	ds DNA	SLE
Speckled	saline extractable antigens Sm	SLE
	SS-A, SS-B	Sjögren's Syndrome
	Scl-70	Progressive systemic sclerosis
	RNP	Mixed connective tissue disease, SLE
Nucleolar	Nucleolar RNA	SLE, scleroderma
Centromere	Centromere/kinetochore region of chromosome	Crest subset of systemic sclerosis

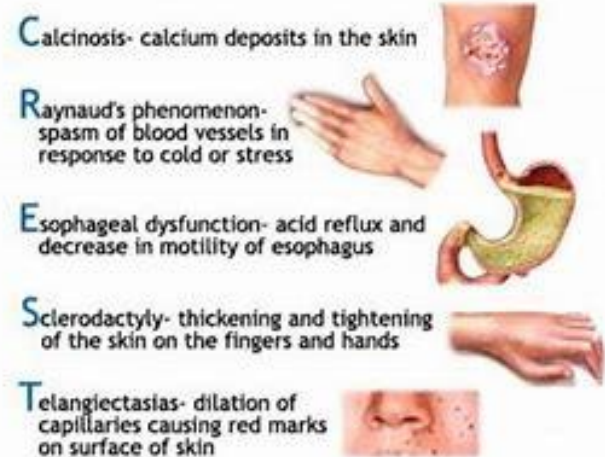
Scleroderma Antibodies

- There are three main antibodies associated with this disease:
 - anti-Centromere limited to fingers and hands
 - anti-Scl 70 diffuse lung disease ILD
 - anti-RNA polymerase III more renal crisis
- Although not exclusive they can be predictors of morbidity and mortality associated with kidney and lung disease

Anti-Centromere Antibody Specificity

- Limited CREST 10-50%
- Diffuse SSC 10-15%
- Rare in Active SLE
- Primary Biliary Cirrhosis

CREST syndrome



Anti-SCL 70 or Topoisomerase Antibody

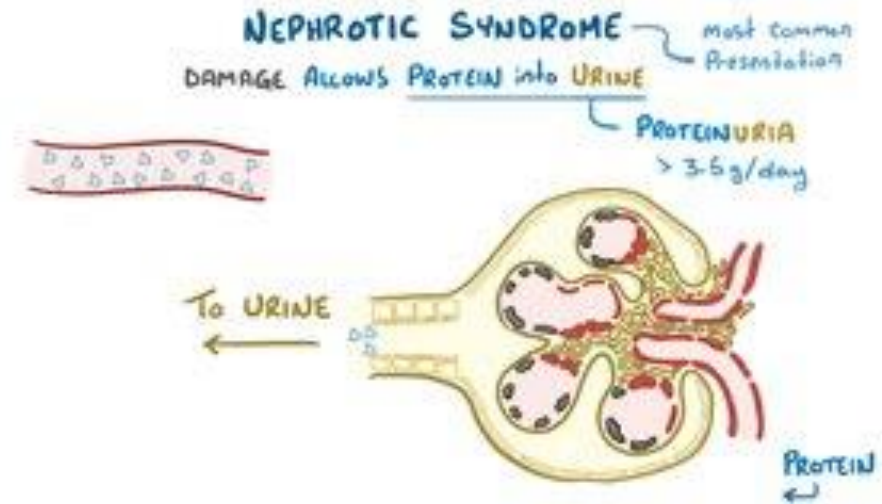
- Diffuse SSC 20%
- Primary limited Sjogren's 10 %
- May be associated with ILD
- Usually run with anti-centromere
- Be sure check anti-SSA and anti-SB
- Polymyositis
- Overlap Syndrome

anti-RNA polymerase III

- Specific marker for Systemic Sclerosis
- Rapid onset sometime after the diagnosis of Raynaud's
- Severe skin thickening
- Often this antibody can be a stand alone
- Often associated with hypertensive renal disease

Anti-Smith Antibody Specificity

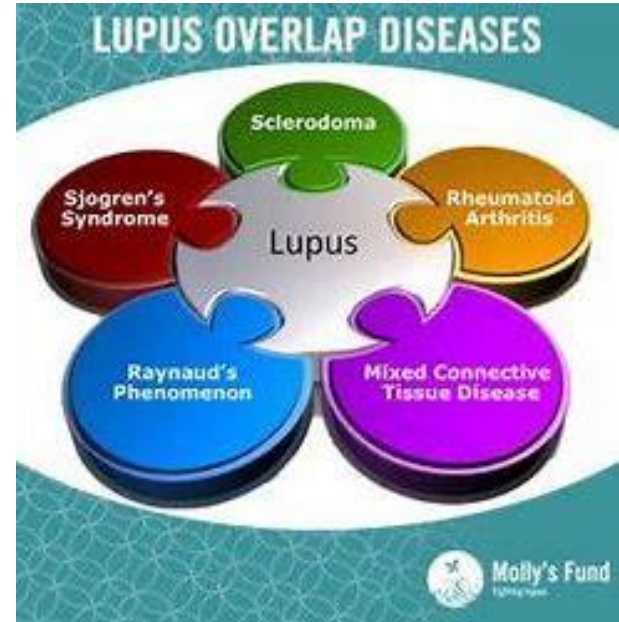
- Only SLE 30%
- Very High Specificity
SLE 95%-99%
- More severe disease
- More CNS, Pul HTN
- Pericarditis
- More renal involvement



Anti-RNP Antibody Usually Tested With Smith

- SLE 30% alone
- **MCTD 95% high titer**
- Drug induced SLE 10-20%
- Limited CREST 2%-14%
- Occ Myositis & RA
- Drug induced SLE 10-20%

If Smith & RNP+ Smith rx to
treatment RNP will remain

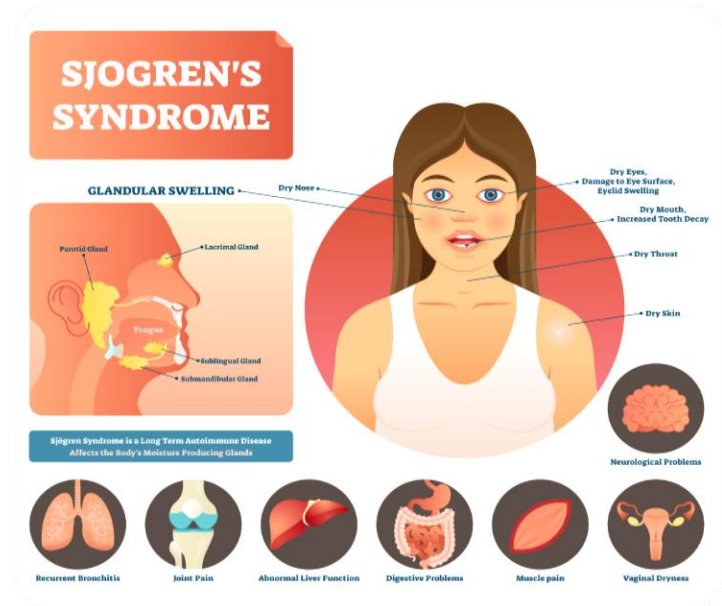


Anti-RNA III vs Anti RNP

- Anti-RNA polymerase III:
 - More cutaneous
 - More scleroderma renal crisis
 - Possible malignancy
 - Myositis
 - Joint contractures
- Anti-RNP: No other antibodies MCTD
 - Digital ischemia
 - Pulmonary Hypertension
 - GERD
 - Sclerodactyl

Anti-Ro SSA and Anti-La SSB Antibody Specificity

- SLE 30%
- Primary Sjogren 88%-96%
- Subcutaneous Lupus Erythematosus
 - Papulosquamous usually annular
- **SSB alone percentage 70-80%: Sjogren's**
- EARLY DIAGNOSIS: BEFORE SLE ANTIBODIES
- Neonatal SLE: mom may be asymptomatic, but baby may have Congenital Heart Block/Rash
- If both Ro and La are positive
 - Most likely with positive LUPUS
 - Increased incidence of Vasculitis
 - Lymphoma

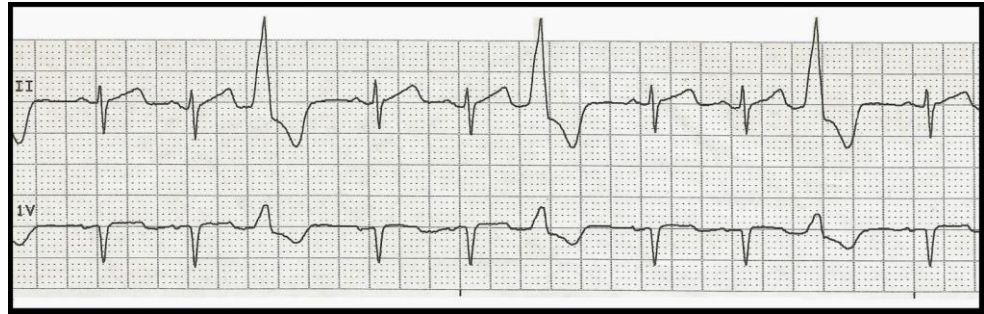


Anti-Histone Antibody Specificity

- Active SLE- 24-95%
- RA 20%
- Scleroderma
- +++ Drug induced SLE bp meds such as Hydralazine 60-100%
- Anti-TNF α Induced

Anti-Chromatin Antibody

- Active SLE 50-90%
- Can be marker for Neuropathy
- Increased sensitivity
 - Drug induced SLE In
 - 50% w Hydralazine
 - 90 with Procainamide



LUPUS Antibodies Summary

Lupus Antibody	Significance
ANA	- SLE
Anti-dsDNA & anti- Smith	+ usually SLE: with treatment dsDNA will decrease
Anti- SSA SSB/Chromatin, RNP	if one + w +ANA increase likelihood of SLE
Anti-RNP	+ for SLE but also scleroderma, inflammatory myopathy possible MCTD
Anti-SSA&SSB	Only 2 + consider Sjogren's w SLE+ RA+ for sure w symptoms
Anti-histone	Sensitivity high for drug induced SLE: if negative not drug induced can be + RA & MCTD and also scleroderma

Case Study

54 year old man with history of HTN managed with Hydralazine.

He has pain, swelling of MCP and am stiffness.

Labs: ANA, anti-chromatin, anti-RNP and anti-Histone are positive.

Diagnosis: drug induced SLE

Warning symptoms may persist for a while even if the medications is DCed

One More:

24 year old African American with a three-month history of malar rash and MCP swelling, am pain and stiffness that resolves through day

LABS: Positive ANA, anti-Chromatin and anti- Smith. Anti-Ds DNA is negative

Diagnosis: SLE but less likely renal problems

Complements

- Elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)
 - Measure of inflammation in the body
- Decreased C3 and C4 serum complement
 - Shows impending or current “flare” of lupus symptoms

Elevated LFT?

- Labs: Certainly, Hepatitis Panel
- Hep B:
 - Surface Antigen + current chronic or acute infection (consider antivirals)
 - Surface Antibody: immunity either vaccine or had the disease and recovered
 - Hep B Core: exposure check for Hep B DNA
- Hep C:
 - Positive IgM acute infection
 - Positive IgG chronic infection
 - Past infection: permanent liver damage

Hepatitis Basic Labs for Any Patient Considering Biologics

	HBsAg	Anti-HBs	Anti-HBc
Susceptible	Negative	Negative	Negative
Vaccinated	Negative	Positive	Negative
Past Infection	Negative	Positive	Positive
Acute Infection	Positive	Negative	IgM Positive
Chronic Infection	Positive	Negative	IgG Positive

Anti Smooth Antibody

- Chronic immune Hepatitis check for high IgG
- Cirrhosis: is there positive Hep B core+ (exposure)
- Infectious Mono
- Might look at Antimitochondrial antibody also:
 - For primary biliary cirrhosis
 - Auto immune hepatitis
 - Cardiomyopathy that can cause cirrhosis (BNP)
 - SLE

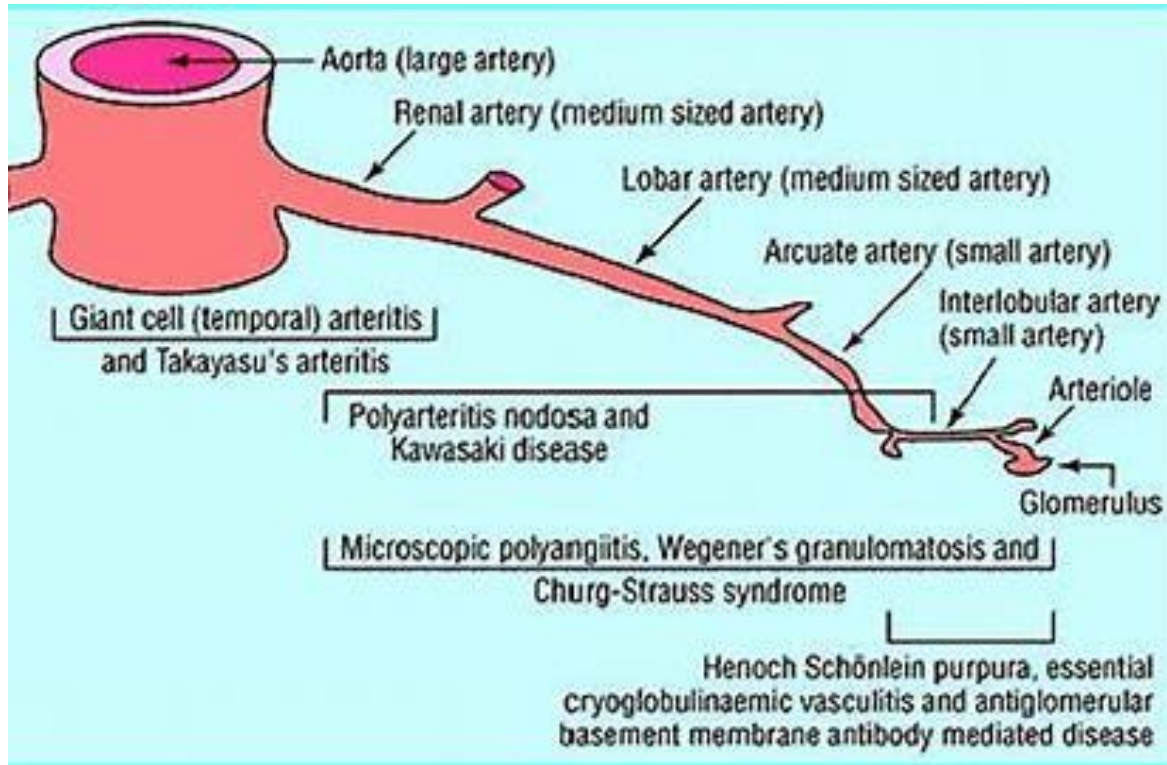
Anti-Mitochondrial Antibody

- Autoimmune hepatitis
- SLE
- RA graft vs host disease
- Usually run with anti Smooth disease in the presence of elevated LFT
- Primary Biliary Cirrhosis
- Primary Biliary Cholangitis

Anti-Phospholipid Antibody Syndrome

- Autoimmune Clotting disorder against three phospholipid antigens:
- Can be venous or arterial thrombosis
- SLE patient have risk of thrombosis but do not have to have SLE to have lupus anticoagulant!
- Important to correlate thrombotic even or miscarriage
- Clotting dyscrasia
 - Two other antibodies
 - Anti-beta 2 glycoprotein
 - Anti-cardiolipin

Vasculitis



ANCA Predictive Value

- ANCA: revolutionized diagnosis of vasculitis
- High Specificity and Sensitivity
- There is huge problems with interpretation
- False positives are a problems for Rare diseases
- General population less than .01% have vasculitis
- Remember is ANCA is negative: most likely don't need to hunt for further screenings: **BUT DO EXAMINE** the patient that is what we are so good at!!!

Vasculitis Mostly Exam: But a Few Labs!!

- GCA: classic symptoms of headache and jaw claudication:
 - Very Elevated inflammatory markers
- PMR: elevated Inflammatory markers with proximal muscle pain++ responsive to steroids
- PAN: Polyarteritis Nodosum: medium arteries + OB stools, + foot drop, flank and pain associated with + Hep B (if had vaccine rare)
- CNS vasculitis: rare antiphospholipid should not cause narrowing of CNS Blood vessels: Check for neurosyphilis and herpes zoster and of course a biopsy is definitive diagnosis

Anti-Neutrophil Cytoplasmic Antibodies (ANCA)

- Detects specific antigen in cytoplasm
- P-ANCA if is positive it may correlate with:
 - Microscopic Polyangiitis
 - Churg-Strauss: predominant pulmonary
 - IBD
 - Drugs may cause a positive result, but not be a true vasculitis: Cocaine, Hydralazine (BP) and Propothioracil used for Graves Disease
 - Not common with Polyarteritis Nodosa (PAN)
- C- ANCA
 - Commonly associated with Granulomatosis with Polyangiitis (GPA)
 - 90% Sensitive and Specific
 - May or may not correlate with disease

GPA vs MPA vs EPA

- GPA (Granulomatosis with Polyangiitis)
 - Is clinically associated with ear, nose, throat, renal and occasionally with gut. A positive C ANCA and PR3 involves small to medium vessels.
- MPA (Microscopic Polyangiitis)
 - Is clinically associated with renal and lung. A positive P ANCA and MPO involves small vessels and capillaries.
- Pauci immune staining can help delineate renal disease in GPA and MPA.
- EPA (Eosinophilia Granulomatosis with Polyangiitis) old name was Churg Strauss.
 - Predominantly associated with pulmonary and occasionally cardiac disease.
 - Eosinophilia only half of the patients have positive P ANCA and MPO.
 - SOB, wheezing and pulmonary desaturation (kinda a lab test).
 - BNP is used to indicate cardiac involvement.
- Biopsy maybe necessary to confirm specific diagnosis.

ANCA Not Associated With Vasculitis

- Cryoglobulinemic Vasculitis
 - Cryoglobulins: healthy people have low level of cryoglobulins
 - Increased Levels are associated with monoclonal gammopathy, SLE and Sjogren's
 - Cryoglobulinemia causes:
 - Multiple myeloma or Hep C
 - Vasculitis: thrombi in the tissue positive both IgM IgG
 - Glomerulonephritis
 - Sensory and motor loss as seen in ANCA+ vasculitis

Case Studies

- 30 year old female chronic sinusitis for ten months treated with multiple tracheal dilatations. She was being treated at a University Hospital. Now presents with right elbow pain. She denies any rashes, fevers or changes in urination.
- Labs: positive C ANCA and PR3. Chest x-ray, UA and CMP within normal limits.
- **Diagnosis: GPA**
- 16 year old African American male drummer for high school, presents extreme fatigue, 16 lbs weight loss, recent SOB, hematuria, periorbital edema and 2+ pitting edema in the feet (my neighbor!!!).
- Labs: Positive C ANCA, MPO and hematuria. Low H&H, O2 saturation 88%.
- **Diagnosis MPA** life threatening renal biopsy full pulmonary workup.

Creatinine Kinase

- Most important lab value for:
 - Polymyositis hint if CK negative check Jo-1
 - LFT due to leakage of damaged muscles
 - Check TSH make sure it is not Hashimoto's Thyroiditis
 - HMG-COA (anti-3 hydroxy-3 methylglutaryl coenzyme)
 - Statin induced inflammatory necrotizing myopathy
 - Stop statin to avoid rhabdomyolysis
 - Dermatomyositis: check for underlying malignancy CEA
 - Many dermatological assessments:
 - Heliotrope rash
 - Shawl sign
 - Gottron's papules
 - Holster sign

Case Study

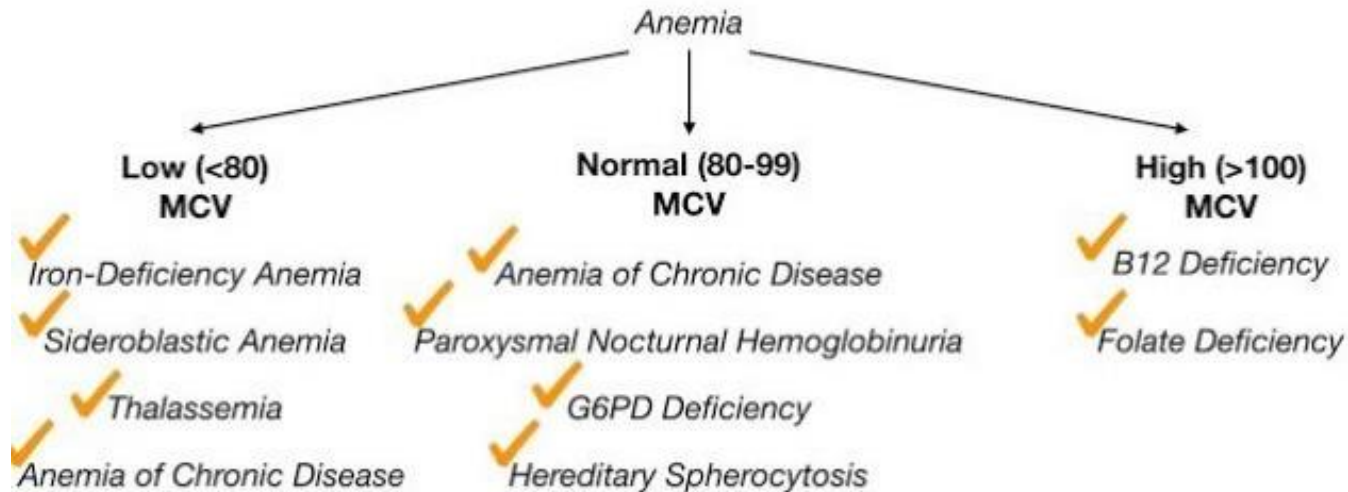
- Patient's husband called because his wife was so weak she could not get off the toilet:
 - She has progressive muscle weakness
 - Purplish color on her eyelids
 - Reported to me that it might be eye shadow
 - No respiratory distress
 - Labs: CK was 16,000 and CEA was negative
- **Diagnosis: Dermatomyositis**

Anemia of Chronic Disease Is Not a New Concept...But

- Types of Anemia:
 - Aplastic anemia: bone marrow failure
 - Iron Deficiency: caused by bleeding or heavy menses
 - Hemolytic: RBC destroyed shorten life span
 - Pernicious: B12 deficiency
 - Anemia is not new to us in Rheumatology: anemia of Chronic Disease but when to intervene?
- Medicare does not let us infuse until HgB is below 7!!!

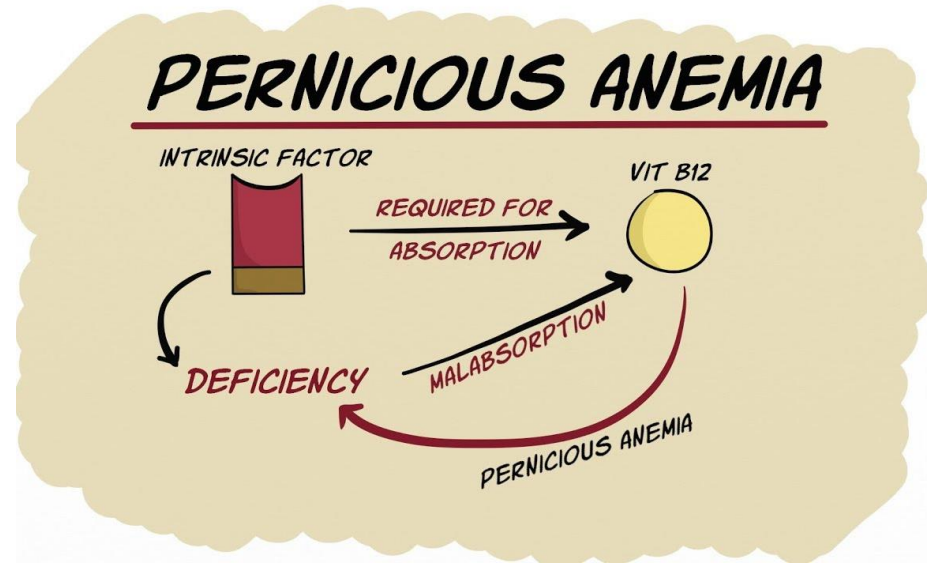
Anemias

Overview



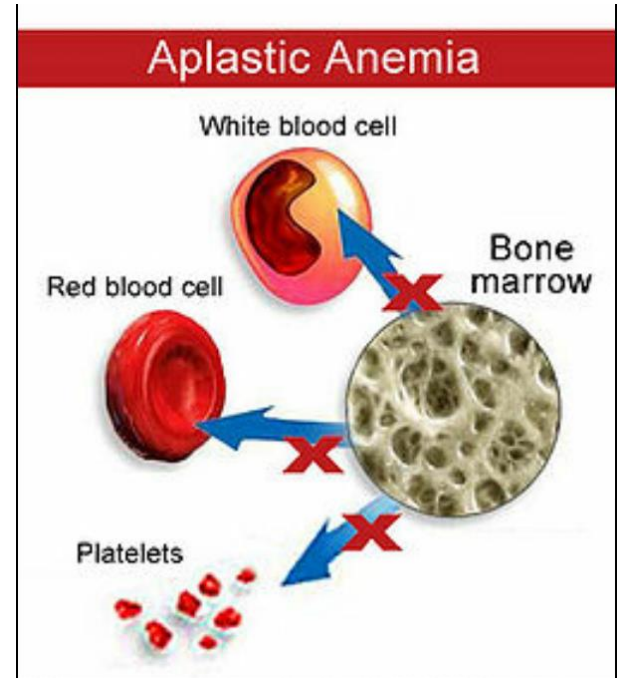
Pernicious Anemia

- Lack of B12
 - Lack of Intrinsic Factor
 - Labs:
 - Haptoglobin, HCT and HBG decreased
 - Bilirubin elevated
 - Who is at risk?
 - Bariatric patient
 - Crohn's
 - Ulcerative Colitis
 - Remember the Gut produces 60% of our immune microbiome



Aplastic Anemia

- Bone Marrow failure: rare
- Labs: low H&H
- Low Reticulocyte count
- Check LFT
- Low platelets
- Low folate levels



Iron Deficiency Anemia

- Caused by:
 - Heavy menses
 - Bleeding
 - SLE changes hemostasis of Fe (anemia of Chronic disease)
 - Poor absorption: again Bariatric surgery, Crohn's, Ulcerative Colitis
- Labs: TIBC elevated due to cells trying to make more transferrin
 - Low FE
 - Low Ferritin
 - Low Reticulocyte Count

Hemolytic Anemia

- Red cells do not have normal life span
- Decreased erythropoietin
- Increased acidosis: reduces Bicarb, red cells die in 5 days instead of 120 days
- Meds that can cause it: PCN, Dapsone, Cephalosporins
- Anemia of Chronic Disease: NSAIDS, Steroids
- SLE and RA Cytokines increase Heparin and increase acute phase reactants, which can mimic Fe deficiency
- Labs:
 - Low H&H
 - Increased bilirubin
 - G6PD deficiency
 - Low reticulocyte
 - Coombs antibodies destroy RBC (Lupus)

Case Study

- 18 year old swimmer suddenly could not do one lap in the pool
- Fatigue, SOB, brain fog, grades starting to fall even though on scholarship for swimming
- Was told tried due to poor diet: more protein, more rest, more green leafy vegetables
- Returned to MD nearly failing, crying, sent her to OBGYN for menses evaluation
- Heavy but only one day out of 7!!
- Sent finally to Hematologist: Labs Increased TIBC but Fe and Ferritin decreased
- **Diagnosis: Iron Deficiency Anemia**

Let's Work It Backwards

Which Lab Would Be Helpful for Diagnosis?

- Ankylosing Spondylitis
- JRA
- Ulcerative colitis, Crohn's
- Psoriatic arthritis
- Reactive RA or Reiter's Syndrome
- Uveitis
 - **Answer: HLA B27.** Note 10-20% of the population may have positive HLA B27 but will have no inflammatory disease

Deductive Thinking

- Overlap Syndrome
- Raynauds
- Inflammatory myopathy
- Fevers
- Mechanic Hands
 - **Answer: anti-Jo-1**

Deductive Thinking

- Skin tightening from finger-tips to wrist only
- Telangiectasia (spider vessels in the face)
- Esophageal dysmotility
- Painful nodules in the hand
- Pulmonary hypertension
 - **Answer: anti-centromere... right again**

More Clinical Deductions

Which Lab Would You Order?

- SLE
- MCTD
- Inflammatory Arthritis
- Scleroderma
- Polymyositis (progressive muscle weakening)
- Raynauds
 - **Answer: anti-Ribonucleoprotein (RNP antibody)**

Positive ANA Can Be All: Back to the Beginning!!

SLE

SCERODERMA

RA

Hashimoto Thyroiditis

Autoimmune Hepatitis

Inflammatory Myopathy

Hep B or Hep C

Medications: Anti-TB, Anti-hypertensive, Anti-hyperthyroid, TNFa

**Answer: 10-20% positive ana with low titer it's
Probably NOT LUPUS!!**

Questions

- Which lab test most specific for SLE of this group:
 - Anti-Smith
 - Anti-Histone
 - Anti-Chromatin
 - Anti-Jo-1
 - Answer: of this group: **anti-Smith. Especially for drug induced SLE**
 - **Anti-Chromatin is not specific as anti-Smith**

More Questions

- Elevated WBC
- Elevated acute phase reactants
- Polyarthropathy (rapidly progressing joint pain)
- Sexually active: that gives it away!
 - **Answer Gonorrhea**

Off to the Caribbean (After COVID)

- Poly articular joint pain
- Mostly MCP
- Elevated WBC
- Elevated acute phase reactants
- Travel to St. Thomas to buy a beautiful sapphire ring!!
 - **Answer: Chikungunya transmitted Aedes Mosquito**
 - Joint pain can last up to 36 months

Most Important

- Clinical diagnosis is not just labs for sure
- Good interviewing techniques are critical
- Telemedicine is here to stay so ask guiding questions
- Sometimes we order labs before the patient's first appointment
- Some of my favorites in no particular order:

Lupus Panel

CBC

RA Panel

CMP

Hep Panel

ESR

TSH

CRP

SPEP

ANA

QuantiFERON

UA

Complements

Specific antibodies based on symptomatology

- My favorite first visit is when they say:
I did not have time to do the LABS!!!!

Major References

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