RHEUMATOLOGY LABORATORY INTERPRETATION AND MONITORING

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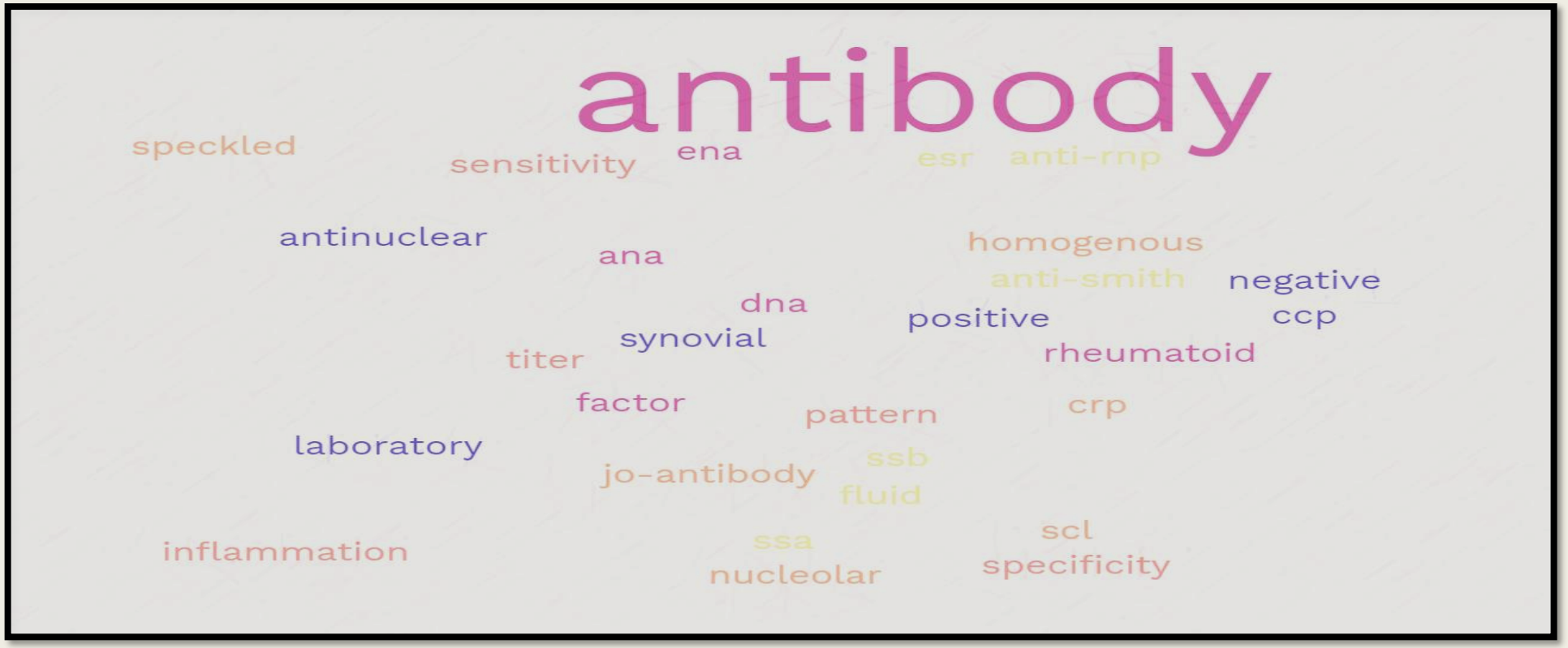
RHEUMATOLOGY LABORATORY INTERPRETATION

Susan Chrostowski



WHAT DETERMINES SIGNIFICANCE?

- **Sensitivity** – percentage of diseased population with positive results (100% sensitive if every person with the disease tests positive)
- **Specificity** – percentage of non-diseased (reference or normal) population with negative test results (100% specific if every person who does NOT have the disease tests negative)
- **Positive Predictive value** – probability of having a disease after a positive test result (Ideal=100%)
- **Negative Predictive value** – probability that a subject does NOT have the disease after a negative test result (Ideal=100%)

(Prinzi, 2020; Wener, 2021)

WHAT DETERMINES SIGNIFICANCE?

- **Likelihood ratio of a positive test (LR+)** = sensitivity/(100%-specificity) = ratio of the proportion of positive tests in those with disease to the proportion of positive tests in those without disease. Excellent test is >10, moderate is 5-10.
- **Likelihood ratio of a negative test (LR-)** = (100% - sensitivity)/specificity = ratio of the proportion of negative test results among disease to the proportion of negative results in those without disease. Excellent test is <0.1, moderate is 0.1-0.2.

(Wener, 2021)

AUTOANTIBODIES

- Antibodies are encoded by immunoglobulin genes
- Autoantibodies arise because of a loss of self-tolerance, leading to reactivity of immunoglobulins against self-antigens
- Certain autoantibody targets are characteristic of distinct autoimmune rheumatic diseases
- The presence of autoantibodies can precede diagnosis (sometimes by up to a decade)
- Benign autoimmunity - false-positive autoantibody results in subjects without disease

(Wener, 2021)

SAMPLE CASE #1

A 33-year-old woman presents to the clinic with complaint of fatigue. She has a family history of systemic lupus erythematosus in her maternal aunt. She is worried about having lupus because of her family history and is asking to be tested.

(Photo © Susan Chrostowski)

Would testing for antinuclear antibody be reasonable?

ANTINUCLEAR ANTIBODY (ANA)

- Test for autoantibody to nuclear antigen
- Positive ANAs are found in 5% of adults and in up to 14% of elderly or chronically ill individuals.
- The ANA test is very sensitive, but poorly specific for lupus, as only 1-2% of all positive results will be caused by lupus alone.
- Results reported in a titer with >1:160 being significant
- The interpretation of a positive ANA test may depend on the magnitude of the titer and the pattern of immunofluorescence.

(Cush, 2018)

AUTOIMMUNE CONDITIONS PRODUCING POSITIVE ANTINUCLEAR ANTIBODY

CONDITION	PERCENTAGE
Hashimoto’s Thyroiditis	50%
Grave’s Disease	50%
Autoimmune Hepatitis	70%
Primary Biliary Cirrhosis	50-70%

(Suresh, 2019)

OTHER CONDITIONS PRODUCING A POSITIVE ANTINUCLEAR ANTIBODY

INFECTIOUS DISEASES - VIRAL	MALIGNANCIES
• Epstein-Barr virus • Human immunodeficiency virus • Hepatitis C virus • Parvovirus 19	• Lymphoproliferative diseases • Paraneoplastic syndromes
INFECTIOUS DISEASES - BACTERIAL	**MISCELLANEOUS DISEASES**
• Subacute Bacterial Endocarditis • Syphilis	• Inflammatory bowel disease • Interstitial pulmonary fibrosis

(Bloch, 2022)

ANA PATTERNS

- Speckled – usually associated with extractable nuclear antigens
- Homogenous – non-specific
- Nucleolar – scleroderma-related
- Centromere – limited scleroderma (CREST syndrome)
- Cytoplasmic – Ribosomal P, Jo-1, and other antisynthetase antibodies

*Different staining patterns are caused by antibodies reacting with specific antigens whose distributions within the nucleus are reflected by the patterns.

(Wener, 2021)

EXTRACTABLE NUCLEAR ANTIGENS (ENA)

ANTIBODY	DISEASE
RNP	Mixed Connective Tissue Disease
SM	Systemic lupus erythematosus
SSA (Ro)	Sjogren’s syndrome
SSB (La)	Sjogren’s syndrome
JO-1	Dermatomyositis/Polymyositis
SCL-70	Systemic sclerosis

(Wener, 2021)

DOUBLE-STRANDED DNA (dsDNA)

- ONLY found in lupus patients
- 30-50% of lupus patients are negative
- Correlates with higher incidence of renal involvement

ANTI-HISTONE

- Drug-induced lupus
  - *Hydralazine*
  - *Minocycline*
  - *Isoniazid*
  - *Procainamide*
  - *Quinidine*
  - *Tumor-necrosis factor (TNF) alpha inhibitors*

(MedlinePlus, 2022)

LUPUS PANEL

	NAME	VALUE	REFERENCE RANGE
F	**ANAIFA QL**	**Positive A**	**Negative;Indeterminate at 1:80**
F	**ANA_TITER QL**	**1:1280 A**	**Negative at 1:160**
F	**ANA PAT QL**	**Speckled A**	**No pattern visible**
F	ANA_TITER QL 2	N/A	Negative at 1:160;N/A
F	ANA PAT QL 2	N/A	No pattern visible;N/A
F	C3	122	49-197 (MG/DL)
F	C4	13	6-42 (MG/DL)
F	DNA	Negative	Negative
F	DNA_TIT	Negative at 1:20	Negative at 1:20
F	**ENA Screen QL**	**Positive A**	
-	Reference Range: ENA SCREEN - Negative is <=20; Positive is >20		
F	ENA_SM QL	13 Negative	Negative
-	Reference Range: Anti Sm :- Neg is <=20; Weak Positive is 21-40; Moderate Positive is 41-80; Strong Positive is >80		
F	**ENA_RNP QL**	**105 Strong Positive A**	**Negative**
-	Reference Range: Anti RNP :- Neg is <=20; Weak Positive is 21-40; Moderate Positive is 41-80; Strong Positive is >80		
F	ENA_SSA QL	4 Negative	Negative
-	Reference Range: Anti SS-A :- Neg is <=20; Weak Positive is 21-40; Moderate Positive is 41-80; Strong Positive is >80		
F	ENA_SSB QL	6 Negative	Negative
-	Reference Range: Anti SS-B :-Neg is <=20; Weak Positive is 21-40; Moderate Positive is 41-80; Strong Positive is >80		
F	ENA_SCL QL	4 Negative	Negative
-	Reference Range: Anti Scl-70 :- Neg is <=20; Weak Positive is 21-40; Moderate Positive is 41-80; Strong Positive is >80		
F	ENA_JO QL	2 Negative	Negative
-	Reference Range: Anti Jo-1 :- Neg is <=20; Weak Positive is 21-40; Moderate Positive is 41-80; Strong Positive is >80		

LUPUS PANEL

	NAME	VALUE	REFERENCE RANGE
F	**ANA**	**Positive A**	**Negative**
- Methodology is Indirect Immunofluorescent Assay (IFA) with a titering system using Hep2000 cells (Hep2 cells transfected with SS-A/Ro)			
F	**ANA_TITER**	**1:1280 A**	**Negative at 1:160**
F	**ANA PAT**	**Mixed:Homogeneous,Speckeled A**	**No pattern visible**
- Methodology is Indirect Immunofluorescent Assay (IFA) with a titering system using Hep2000 cells (Hep2 cells transfected with SS-A/Ro)			
F	C3	95	49-197 (MG/DL)
F	C4	15	6-42 (MG/DL)
F	DNA	Negative	Negative
F	DNA_TIT	Negative at 1:20	Negative at 1:20
F	**ENA Screen**	**Positive A**	
F	ENA_SM	2 Negative	Negative
F	ENA_RNP	2 Negative	Negative
F	**ENA_SSA**	**33 Weak Positive A**	**Negative**
F	ENA_SSB	2 Negative	Negative
C	ENA_JO	4 Negative	Negative
F	ENA_SCL	4 Negative	Negative

SAMPLE CASE #1 DISCUSSION

- Our patient does not have any joint pain, skin rashes, oral ulcers, sicca symptoms, or Raynaud phenomenon. Findings on physical examination and urinalysis are unremarkable.
- The provider decides to check a CBC, ESR and TSH. Although the patient is reassured that her fatigue is not due to lupus, she insists on getting a lupus test.

SAMPLE CASE #1 DISCUSSION

LUPUS PANEL

Component	Finding	Reference Range
ANAIFA QL	**Positive**	Negative
ANA_TITER QL	**1:80**	Negative
ANA PAT QL	Homogenous	No pattern visible
ANA_TITER QL 2	N/A	Negative at 1:160; N/A
ANA PAT QL 2	N/A	No pattern visible; N/A
C3	150	49-197 mg/dL
C4	23	6-42 mg/dL
DNA	Negative	Negative
DNA_TIT	Negative at 1:20	Negative at 1:20
ENA Screen QL	Negative	
ENA_SM QL	Negative	Negative
ENA_RNP QL	Negative	Negative
ENA_SSA QL	Negative	Negative
ENA_SSB QL	Negative	Negative
ENA_SCL QL	Negative	Negative
ENA_JO QL	Negative	Negative

SAMPLE CASE #1 DISCUSSION

- CBC is normal.
- ESR is 6 mm/hour – also normal.
- TSH is elevated. Additional testing showed low free thyroxine and positive thyroid peroxidase antibodies.

What is the conclusion? What do you tell the patient?

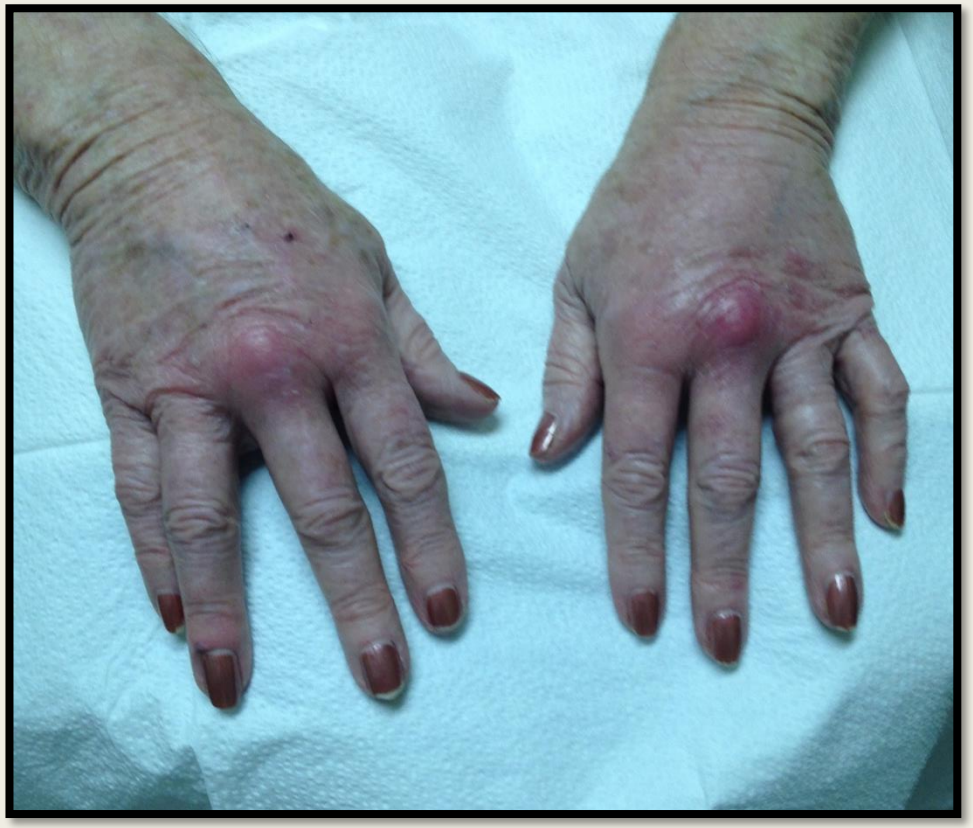
RHEUMATOID FACTOR

- Autoantibody directed against Fc portion of IgG (the main immunoglobulin in normal serum).
- Estimated rheumatoid arthritis sensitivity is 69% and specificity is 85%
- Rheumatoid arthritis diagnosis cannot be confirmed or excluded just based on testing result.
- Numerous other conditions can produce a positive result.

(Suresh, 2019; Wener, 2021)

SAMPLE CASE #2

A 76-year-old female presents to the clinic with a 2-day history of acute pain and swelling in both hands over the MCP joints. She has never had this before. No one in her family has a history of inflammatory arthritis and she has not had any recent illnesses.



(Photo © Susan Chrostowski)

What testing should be considered?

CONDITIONS PRODUCING POSITIVE RHEUMATOID FACTOR

CONDITION	PERCENTAGE
Rheumatoid arthritis	70%
Primary Sjogren Syndrome	75-90%
Infective endocarditis	40%
Hepatitis C	76%
Mixed Cryoglobulinemia	100%
Primary Biliary Cirrhosis	45-70%
Healthy People	5-25%

(Suresh, 2019)

CCP-ANTIBODY OR ACPA

- Antibodies to citrullinated peptide/protein antigen (ACPA), also called anti-CCP.
- Sensitivity is 67% (similar to Rheumatoid Factor)
- Specificity is 95% (higher than Rheumatoid Factor)
- Likelihood ratio = 12.5
- Occur rarely in other autoimmune disorders
- Moderate to high titers of ACPA are prognostically associated with more severe disease

(Wener, 2021)

SAMPLE CASE #2 DISCUSSION

- Diagnostic criteria for rheumatoid arthritis requires at least 1 joint with definite clinical synovitis with the synovitis not better explained by another disease.
- Additional criteria are based on numerical scores related to:
  - *The joints involved (large or small)*
  - *Serology (RF and Anti-CCP)*
  - *Acute phase reactants (ESR and CRP)*
  - *Duration of symptoms*

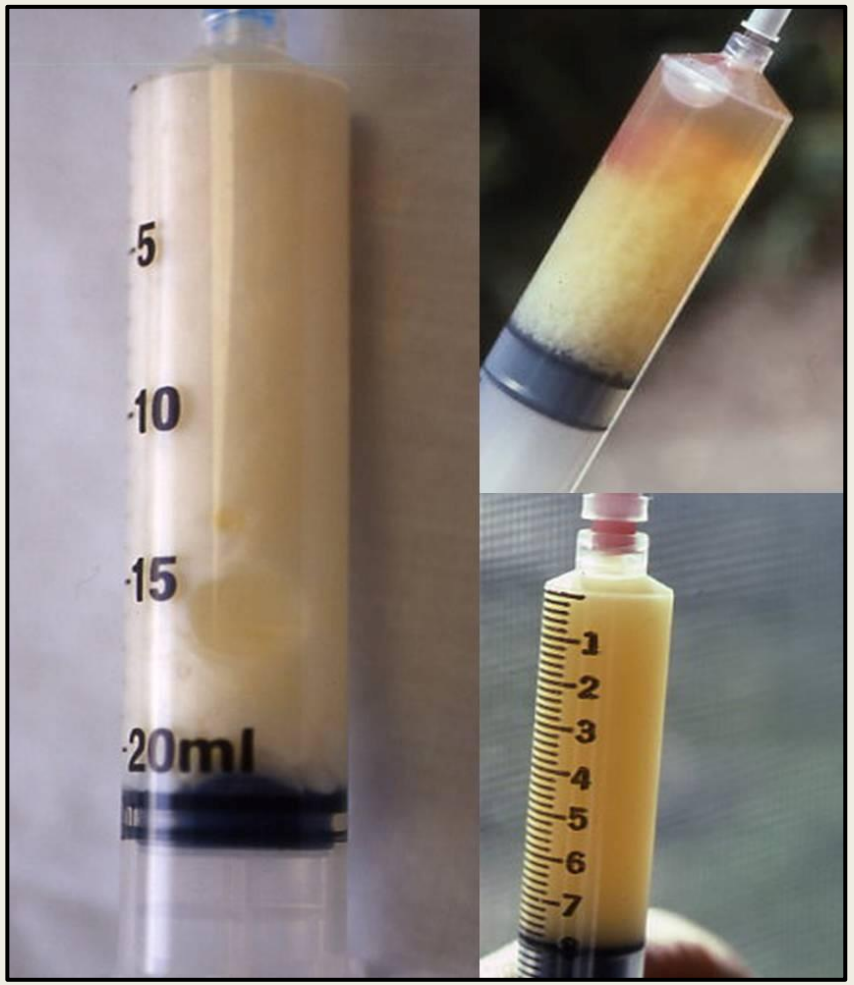
SAMPLE CASE #2 DISCUSSION

LAB	RESULT	REFERENCE
Rheumatoid Factor	11 (negative)	<14 IU/mL
Anti CCP	<17 (negative)	<17 U/mL
ESR	**111 (high)**	0-20 mm/hr
CRP	**10.3 (high)**	0.8 mg/dL
Uric acid	4.4 (negative)	2.6-7.2 mg/dL
ANA, dsDNA, ENA	Negative	
Neutrophilic cytoplasmic IgG	**1:2560 (high)**	<1:10

What is the conclusion? What do you tell the patient?

SYNOVIAL FLUID ANALYSIS

- Viscosity
- Color and clarity
- Cell count
- Crystals
- Gram stain and culture



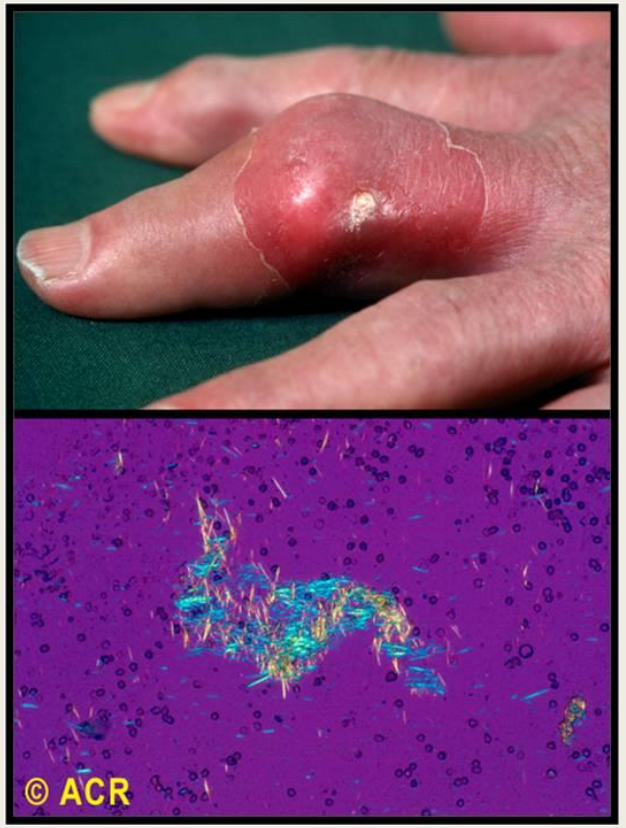
SYNOVIAL FLUID ANALYSIS

CHARACTERISTIC	NORMAL	NONINFLAMMATORY	INFLAMMATORY	SEPTIC	HEMORRHAGIC
Clarity	Transparent	Transparent	Transparent to opaque	Opaque	Bloody
Color	Clear to yellow	Clear to yellow	Yellow or white	Yellow or white	Red
WBC count	<200/mm^3	<2000/mm^3	2000-50,000/mm^3	>50,000 /mm^3	Variable
PMN leukocyte percentage	<25	<25	>50	>75	50-75
Possible clinical associations		Osteoarthritis Trauma Osteonecrosis	Rheumatoid arthritis, Lupus, Crystalline	Septic arthritis	Trauma, TB, Coagulopathy, Neoplasia

(Adapted from Wu & Dixit, 2021)

CRYSTALS IN SYNOVIAL FLUID

- MSU (monosodium urate) crystals – gout
  - *Sensitivity of >90% when present in acute gout*
- CPPD (calcium pyrophosphate dihydrate) - pseudogout
- Hydroxyapatite or basic calcium phosphate (BCP) - osteoarthritis



Important note: The presence of crystals does not rule out infection. Always get the culture!

INFLAMMATORY MARKERS

- Erythrocyte Sedimentation Rate (ESR) – reflects both acute and chronic inflammation
  - *Extreme elevations (greater than 100mm/h) are likely due to infection, malignancy, or autoimmune rheumatic diseases*
  - *Age-adjusted values: Women = age + 10 / 2; Men = age / 2*
- C-Reactive Protein (CRP) –
  - *Can be reported in mg/L or mg/dL (BIG difference in results!)*
  - *Age-adjusted values: Women = age + 30 / 5; Men = age / 5*
- Ferritin – can also be considered an acute phase reactant - released from the liver and mononuclear phagocytes during inflammation

(Wener, 2021)

OTHER TESTS

- Antiphospholipid Antibodies – association with thrombotic risk
- Lupus Anticoagulant – associated with thrombosis
- Antineutrophil Cytoplasmic Antibody (ANCA) – vasculitis
  - *Antimyeloperoxidase antibodies – MPO-ANCA*
  - *Antiproteinase 3 antibodies – PR3-ANCA*
- Angiotensin Converting Enzyme (ACE) – sarcoidosis
- HLA-B27 – genetic marker associated with ankylosing spondylitis, reactive arthritis, and inflammatory bowel disease
- Complements – most commonly C3 and C4 – reduced concentrations with SLE flares

(Suresh, 2019; Wu & Dixit, 2021)

CLINICAL PEARLS

- Sometimes disease can be present when the lab is negative and disease can be absent when the lab is positive.
- Laboratory tests should be used to **confirm** a specific clinical diagnosis and not be used to screen or evaluate patients with vague rheumatic complaints.
- 4-5% of healthy individuals will have a positive RF or ANA, but only 1% will actually have rheumatoid arthritis and <0.4% will have lupus.
- The chance of having a benign positive ANA test increases with age (occurs in healthy individuals).
- A highly abnormal test result is more likely to be clinically significant compared to one that is barely abnormal.

(Cush, 2018; Wener 2021)

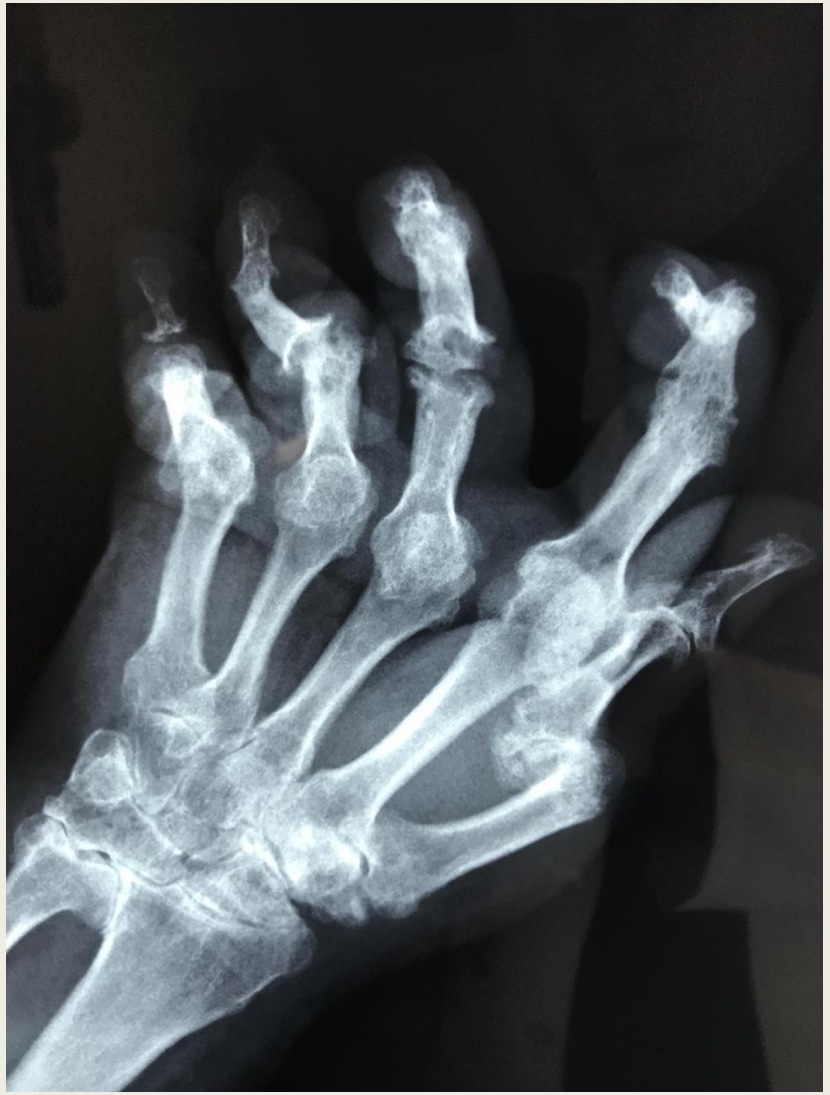
MONITORING PATIENTS ON DMARDS AND BIOLOGICS

Susan Quisenberry

Boxes Checked…What Now?

- Initial work up completed? ☑
- Basic idea of what is going on? ☑
- Referral made to rheumatology? ☑
  - *Patient is being managed by Rheum?* ☑

Whew, My part is done… ☒



CHRONIC INFLAMMATION

Organized attack

Autoimmune Disease: Significance of the Problem

- Affects 5-10% population worldwide
- #1 cause of all cause disability
- Tremendous burden on health care system
- Associated with increase in mortality and morbidity

- Among the 10 leading causes of death (ages <65)
- Leading cause of disability for women in US
- Comorbidity at initial presentation not well known

(Nikiphorou et al., 2017; Simon, et al., 2017)

Autoimmune Disease

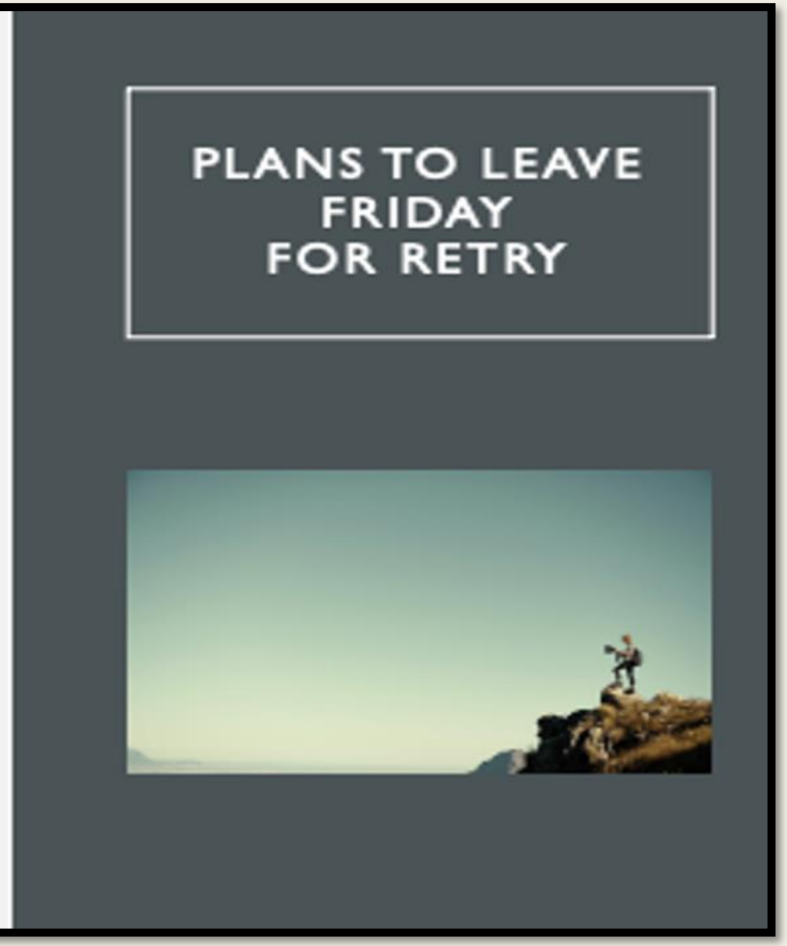
Practice Implications

- Often coexistence of more than one autoimmune disease
  - *AKA ”overlap”*
  - *Psoriasis + association with 14 autoimmune diseases*
- Comorbidities shorten lives
  - *Increase comorbidities in this population*
    - Rheumatoid lung
    - Felty’s syndrome,
    - Vasculitis
    - drug-induced comorbidities
  - *Healthcare disparities*
- Long-term prognosis improved with DMARD and Biologic therapies
  - *PCP: knowledge of medication therapies and potential comorbidities associated with therapy*
  - *Primary and secondary prevention*

(Nikiphorou, 2017; Simon, 2017; Dougadous, 2013)

Case Study

63 y/o white male presents for routine f/u.
Hx Sero + RA (erosive)



CC: Doing great except these pesky mosquito bites on my legs for my hike last week.

ROS:

denies fatigue, fever, rash, CP, SOB, unusual lumps or bumps except the mosquito bites left thigh

Rheum ROS:

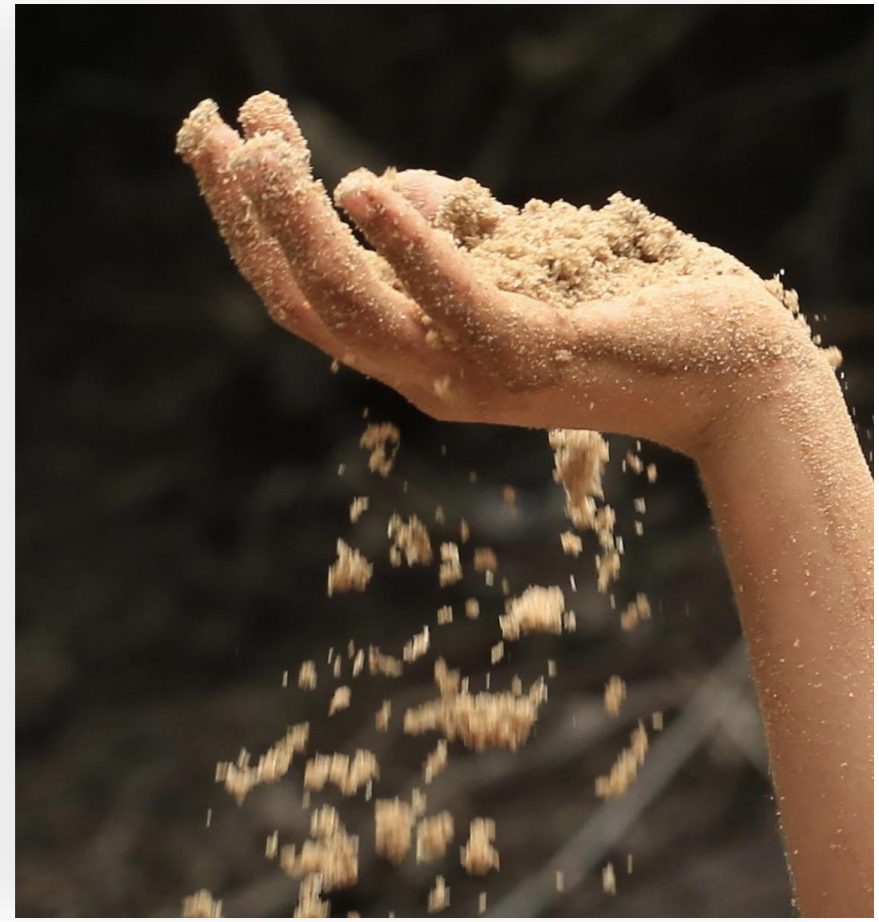
+ Chronic knee pain, denies pain or swelling to hands/feet. Morning stiffness hands/feet ~ 15” duration that improves with minimal activity.

Current Medications

- tofacitinib 11 mg XR/day
- Methotrexate 15 mg/week
- Metformin 1000 mg/day
- folic Acid 1mg/d
- lisinopril 10 mg/d
- ibuprofen 600 mg TID prn
- Medrol dose pack- prn

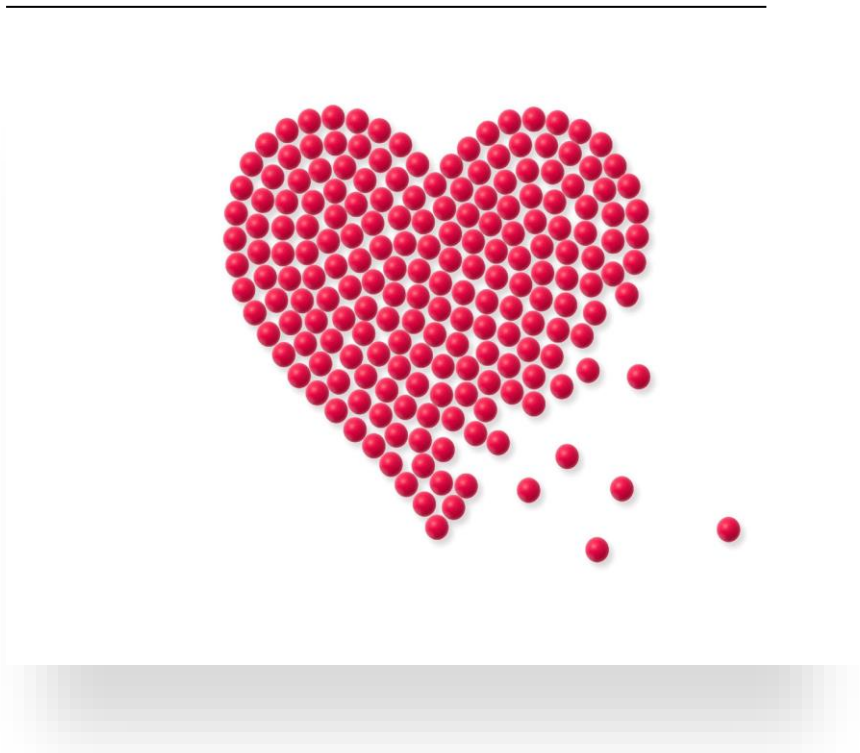
Question of the day….

Rheumatology initiates therapy & Lab….Who identifies and manages the Comorbidity risk related to therapeutics?



Common Comorbid Conditions

- Infection
- Endocrine
- Cardiovascular
- Gastrointestinal
- Pulmonary
- Musculoskeletal
  - *Osteoporosis, Joint deformities*
- Psychosocial
- Disability



MONITORING PATIENTS ON THERAPY

A Primary Care Approach

DMARD Therapy

DMARDS	Classification	Half-life	Adverse Effects	Monitor	BlackBox Warning	Patient Education
Methotrexate	DMARD; antimetabolite (CYP2D6 inhibitor; weak)	3-15 hr	Liver, lung, kidney toxicity, mucosal ulcerations; myelosuppression, oral ulceration, N,V, alopecia	CBC, LFT, Renal, TB (baseline);	Fetal toxicity & death; Bone Marrow suppressin;	2 forms birth control; folate supplement; weekly administration
Hydroxychloraquine (Plaquenil)	DMARD	32-50 day	myelosuppression, retinal toxicity, QT prolongation, Torsades, arrythmias, hypoglcemia, photosensitivity; lowers siezure threshold	Ophthalmic Exam, EKG, CBC (prolonged tx)	none	hypglycemic effects, lowers siezure thresh; sunscreen
leflunomide (Arava)	DMARD	~19 days	Infection, SJS, hepatotoxicity, myelosuppresion, ILD, periph neuropathy; Diarrhea, alopecia, N, D, oral ulcers	CBC, LFT q 2 mo; TB-q (baseline)	Fetal Toxicity, Hepatotoxicity	2 forms birth control. folate supp
sulfasalazine (Azulfidine)	DMARD	7.6 hr	anaphylaxis, SJS, pulmonary toxicity, hepatotoxicity, pancreatitis, infertility, oligospermia (reversible), photsensitivity; stomatitis	CBC, LFT, BUN/CR, UA	none; caution Renal/hepatic impairment	hypoglycemic effects, sunscreen

BIOLOGIC	CLASSIFICATION & MOA	HALF-LIFE	BLACK BOX	ADVERSE EFFECT	MONITOR	PATIENT EDUCATION
Adalimumab (Humira)	a-TNF Inhibits tumor necrosis factor leading to decreased inflammation & cytokine storm	2 wk	Serious infection risk; Malignancy; lymphoma; TB reactivation; Pediatric Cancers CAUTION > 65 y/age, Malignancy risk, CF, myelosuppression, chronic infection, uncontrolled DM	URI, H/A, rash, UTI, hyperlipidemia, abd pain, HTN, hematuria, neutropenia, ALT elev; pancytopenia SERIOUS: TB, HBV, malignancy, lymphoma, CHF, vasculitis, sarcoidosis, ILD, hepatotoxicity, skin cancer	HBsAg, annual TB, Ongoing monitor for infection, CBC, LFT Pediatrics: vaccinations up to date prior to initiation CAUTION in elderly Contraindicated mod/sev HF	Avoid with chronic infection. Suspend w acute infection, Sunscreen. Review risk vs benefit, I inquire HF hx or sx Report flu-like sx (autoantibody development) *Annual screenings and immunizations encouraged (no live vaccines)*
Tocilizumab (Actemra) Indications RA,	IL-6 antagonist Binds to IL-6 receptors; decreases inflammation and alters immune response	5-13 days	Serious infection; TB; Hepatotoxicity; opportunistic infections (some fatal); Caution: active infection; ANC <2000, plt <100; AST/ALT > 1.5 x ULN; hepatic disease, Hx GI perforation risk; demyelinating dz; recurrent infections	*Dyslipidemia, URI, HTN, N/D, ALT/AST elevation;, insomnia, oral ulcer, abd pain, thrombosis* *Serious: TB reactivation; Infection; malignancy, GI perf, pancreatitis, anaphylaxis, hepatotoxicity, acute renal injury; SJS, demyelinating CNS dz; thrombosis*	*TB, LFT, CBC, baseline platelets; lipids, hepatotoxicity; opportunistic infection; malignancy; GI perf, CNS demyelinating dz, hypersensitivity*	*Notify provider for any infection signs & sx; new onset abd pain, fever, extremity swelling, skin rash, neuro changes* *Discuss Increased CV risk; annual screenings and recommended immunizations encouraged (no live vaccines)*

AbbieVie, 2022, Hffman-LaRoche, 2021, AbbVie, 2018, Pfizer, 2014)

Table: Quisenberry, 2022

BIOLOGIC	CLASSIFICATION & MOA	HALF-LIFE	BLACK BOX	ADVERSE EFFECT	MONITOR	PATIENT EDUCATION
Secukinumab (Cosentyx) *Ixekizumab (Taltz)*	*IL-17* *Bind/interferes IL-17 cytokine; reduces inflammation and alters immune response*	*22-31 days*	*Serious infection; Active TB; Invasive fungal infection; hepatoxicity* *Contraindicated serious infection, TB,* *Caution in elderly – (increased adverse effects)*	*Infection, nasopharyngitis, neutropenia, thrombocytopenia, diarrhea, UR; GI perf; Viral reactivation; Hepatotoxicity* *Serious: Hypersensitivity/anaphylaxis; inflame bowel dz; Serious infection, neutropenia; Sepsis (adults); Toxic Shock syndrome (peds)*	*TB at baseline; then yearly after treatment; LFT; lipids; CBC* *Cardiovascular risk, Malignancy, Hypersensitivity reactions; Demyelinating disorders,*	*No live vaccinations during treatment; Report new onset abd pain; Report any signs or sx of infection, fever* *Annual screenings and immunizations encouraged*
Guselkumab (Tremfya) *$11922.00/inj* *Indication: Psoriasis*	*IL-23 antagonist* *Binds to p19 subunit of IL 23 and inhibits IL 23 cytokine-induced responses including release of pro-inflam cytokines and chemokines*	*15-18 days*	*No Black Box*	*Infection, URI, H/A, Injection site rxn, arthralgia, LFT increase.* *Serious: Hypersensitivity rxn, anaphylaxis, serious infection; TB reactivation*	*TB at baseline and yearly, Monitor for infection (acute and chronic)*	*Report fever or signs of acute or recurrent infection. Annual screenings and immunizations encouraged (no live vaccines)*

BIOLOGIC	CLASSIFICATION & MOA	HALF-LIFE	BLACK BOX	ADVERSE EFFECT	MONITOR	PATIENT EDUCATION
Risankizumab (Skyrizi) (Indications: IBS, Psoriasis ,PsA, SpA)	Binds to p19 subunit of IL-23 & inhibits IL-23 cytokine-induced responses including proinflammatory cytokines	21 days (Crohn's) & 28 days psoriasis	None	Infection (> 1st 16 wks), URI, H/A, Injection site rxn, arthralgia, anemia, back pain, fatigue, inc Lipids, LFT increase; fatigue; fungal infections Serious: Hypersensitivity rxn, anaphylaxis, serious infection; hepatoxicity, hepatic injury (Crohn's); TB reactivation; Avoid if liver cirrhosis	`Crohn's: Monitor ALT, AST, Bilirubin at baseline; TB at baseline;	Avoid live vaccine; completed recommended age-related vaccinations (prior to initiation of possible); Report signs & Sx of viral, bacterial, or tinea infection, fever, cough, sweats, myalgias, Diarrhea, dysuria, skin rash (cellulitis); Pregnancy/Br feeding (not studied)
Rituximab (Rituxan) (Non-Hodgkin's Lymphoma; CLL; RA; Granulomatosis with Polyangiitis;(Wegener's Granulomatosis); Phemigus Vulgaris Off label: Dermatomyositis	`B-cell depletion agent; CD 20 Inhibitor Binds to B-lymphocyte CD20 surface antigens; inducing cell lysis of CD-20 expressing cells.	18-32 days	Fatal infusion reaction within 24 hour (80% occur first dose); Severe mucocutaneous reactions; some fatal; HBV reactivation; Progressive multifocal leukoencephalopathy (PML) resulting in death	HTN; hypotension; nausea, URI; Pruritis; chills; dyspepsia, rhinitis; paresthesia; urticaria; Upper Abd pain; throat irradiation; migraine; anxiety; asthenia. Significant adverse reactions: Infusion reactions; mucocutaneous rx; ep B reactivation with fulminant hepatitis; PML; tumor lysis syndrome; Infection; Cardiovascular adverse reactions; renal toxicity; bowel obstruction & perforation	HBsAg, anti-HBc, pregnancy test as baseline; TB; Monitor for s/sx hepatitis or HBV reactivation; CBC with differential at baseline & every 2-4 months; and prior to redosing treatment Monitor for cardiac arrythmias.	Requires Premedication with antihistamine, acetaminophen, methylprednisolone Avoid live vaccine; completed recommended age-related vaccinations (prior to initiation of possible); Reports S & Sx of infection

BIOLOGIC	CLASSIFICATION & MOA	HALF-LIFE	BLACK BOX	ADVERSE EFFECT	MONITOR	PATIENT EDUCATION
Abatacept (Orencia)	T-cell costimulation Modulator; Immunosuppressant Selectively modulates T-cell activation, altering immune response	13.1-14.3 days	None	Common: H/A; URI; sore throat; back pain; dyspepsia; UTI; N/D; epistaxis; anemia; nasopharyngitis; Serious: Risk of serious Infection; Malignancy; Sepsis; anaphylaxis; Acute pyelonephritis; multiple sclerosis; vasculitis; cellulitis; pneumonia; Basal and squamous cell carcinomas; Viral hepatitis; TB reactivation; hypersensitivity reaction. Reactivation of Hep B; May worsen COPD	Hepatitis panel; TB at baseline; dermatologic exams especially if risk of skin cancer; Sx of Epstein Barr virus; CMV reactivation (post transplant)	May increase blood glucose (contains Maltose); Report sx of infection; worsening COPD sx; Annual skin exam; Avoid live vaccine during and 3 months after dosing; completed Birth Control: pregnancy data unknown.

Hang in there..
Almost done

Case Study Coming Up!

BIOLOGIC	CLASSIFICATION & MOA	HALF-LIFE	BLACK BOX	ADVERSE EFFECT	MONITOR	PATIENT EDUCATION
Tofacitinib, (Zeljanz) Upadacitinib (Rinvoq) baricitinib (Olumiant)	Janus Kinase Inhibitors Inhibits Janus-associated kinases (JAK) 1, 2 and 3 leading to disruption of cytokine and growth factor signaling pathways	3 hrs XR (6-8 hr) Excreted in urine; metabolized in liver Cytochrome P450: 2C19, 3A3 primary substrate	Risk serious infection leading to Hosp and/or death; TB; invasive fungal inf; opportunistic infections; TB reactivation; malignancy, EBV Thrombosis/DVT, arterial thrombosis (> in age 50 and over Higher rate of mortality including sudden CV death if > 50 with 1 CV risk factor (tofacitinib)	Common: URI, inc cholesterol; H/A, Inc CPK; rash; diarrhea; herpes zoster; anemia; nausea; UTI, HTN, AST/ALT elevation; lymphocytosis (transient); inc in Creatinine. Serious: mortality increase; CV death; MI; Stroke; Severe infection; Viral reactivation; malignancy; lymphoma; lung CA; Skin CA; DVT; PE; arterial thrombosis; neutropenia; lymphopenia; hypersensitivity rxn; GI perf; ILD; infertility (animal studies)	TB and hepatitis panel at baseline; Lipids at baseline ad 4-8 weeks after baseline ; CBC at baseline then 4-8 wks after initiation then q 3 months; TB periodically; LFT; derm exams if skin CA risk Use in caution with elderly; lung dz; ILD; zoster hx; HBV carriers; CVD; smokers or past smokers; malignancy; GI Perf risk (diverticulitis); GI stricture; DM; thrombosis risk	Works very fast; may not be appropriate for all. Requires routine lab monitoring Call for any s/sx of infection; LE swelling; abd pain; chest pain (ER); SOB (ER); Birth Control: pregnancy data unknown.

- Indications for Primary Care?
- Maintain a high suspicion for all patients on DMARDs and Biologics

Remember our Case Study?
CC: Doing great except these pesky mosquito bites

ROS:

denies fatigue, fever, rash, CP, SOB, unusual lumps or bumps except the mosquito bites left thigh

Rheum ROS:

+ Chronic knee pain, denies pain or swelling to hands/feet. Morning stiffness hands/feet ~ 15” duration that improves with minimal activity.

Current Medications

- tofacitinib 11 mg XR/day
- Methotrexate 15 mg/week
- Metformin 1000 mg/day
- folic Acid 1mg/d
- lisinopril 10 mg/d
- ibuprofen 600 mg TID prn
- Medrol dose pack- prn

PMH & Social

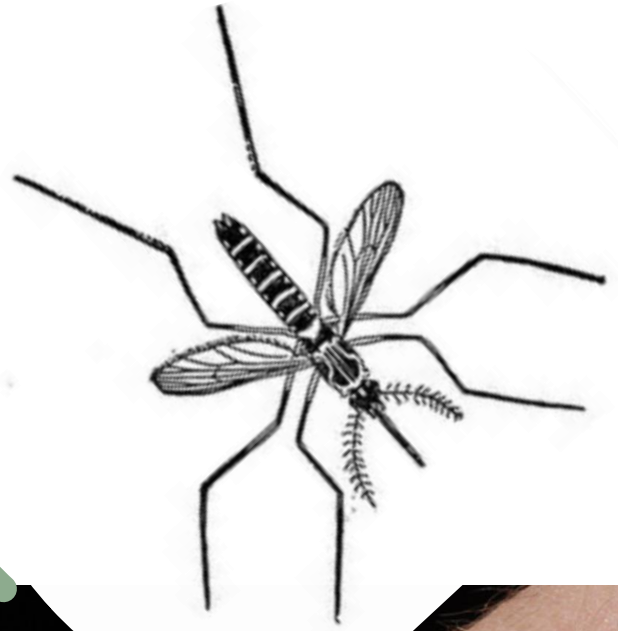
- HTN (on ACE-I, controlled)
- DMII (A1C 7.1)
- OA Knees, L-spine
- Vaccines: Pneumovax, Prevnar 13, Flu, Tetanus

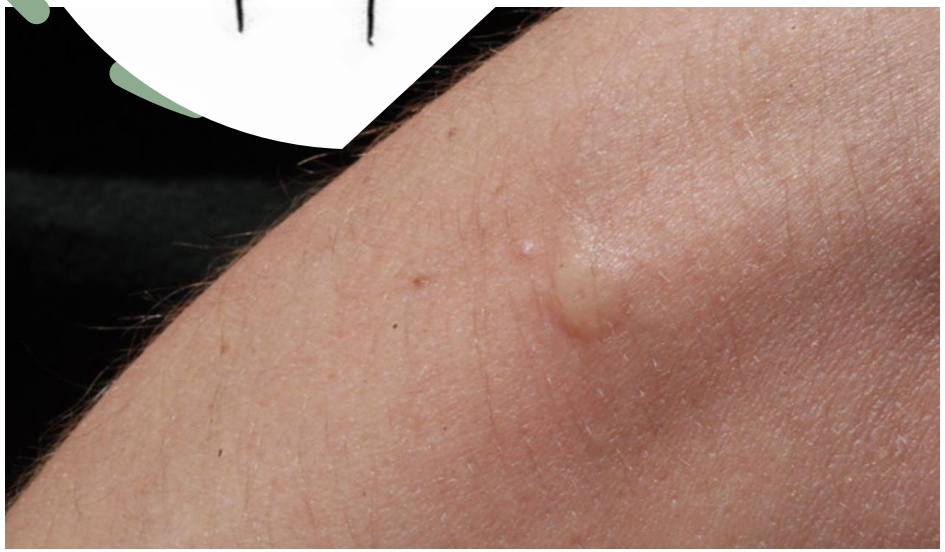
- Family Hx
  - *HTN*
  - *CAD*

- Hiker – Long distance
- Risk Taker – Hx snake bite x 2
- Married x 32 yr
  - *Wife – Fibromyalgia*
- Retired executive

Physical Findings

- BMI-31 BP 142/86 Pulse: 86 RR 15. Pain 0/10
- H/F: No pain/synovitis noted on palpation, full ROM, Knees crepitus.
- Skin: various raised red papules; 3-6 mm diameter, secondary lesions (arms/feet), some erythema, no induration
- CV/PULM: unremarkable
- Neck: No lymphadenopathy, No supraclavicular lymphadenopathy
- MSK: Full ROM, No synovitis, Puffy Left foot noted





What would you do?

Requested a gown to inspect the insect bites to left thigh

Significant increase in diameter left leg compared to right

Inquired about travel…

“I flew to North Carolina Friday to purchase a car and drove it back to Oklahoma over the weekend.”

Referred to ER for stat Venous Duplex study

Dx: Large bilateral Iliofemoral DVT

- Immediate hospitalization
- Required percutaneous aspiration thrombectomy bilaterally x 2

Lifestyle assessment	Health & Malignancy Assessment & Screenings	Immunization & compliance	PCP
• Weight loss • CV exercise • ROM • Smoking cessation • ETOH • Diet Modification	• BMI & Vital Signs • Colonoscopy • Mammography • Dexascan • Lipids, & Framingham risk • Lung assessment • Skin Assessment • GI Assessment • Depression scale	• COVID,-19 • Influenza, • Pneumococcal, Zoster, • Hep B, • Prevnar 13 • ***No Live Virus*** vaccinations if on Biologics	• Medication Reconciliation • Collaborative management with Rheumatology esp with suspected infection • Maintain high alert & suspicion for comorbid conditions

Clinical Pearls

- Autoimmune Dz? Always maintain a high index of suspicion
- Think prevention: Collaborate with Rheumatology provider
- Educate the patient on necessity of routine primary care f/u

Thank you for the hospitality!!!

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