Rheumatology Labs for the General Internist

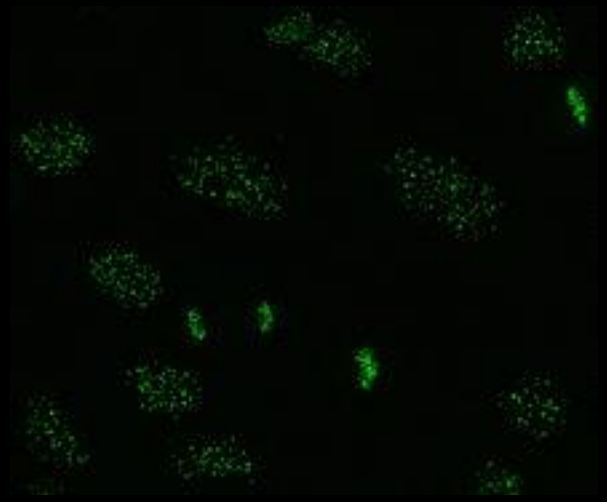
Adam J Grunbaum DO FACOI FACR | ACOI Annual Convention and Scientific Sessions 2018

Disclosures

- No disclosures relevant to the topic.

Objectives

- Understand how specificity and sensitivity of rheumatologic labs affect likelihood underlying of rheumatic disease.
- Understand what constitutes an initial workup in clinical settings of suspected inflammatory arthritis, systemic lupus, myositis, scleroderma and vasculitis.
- Understand which labs may constitute the need for more urgent referral.



So How Diagnostic are Rheumatologic Labs?

Rheumatology Labs – General Concepts

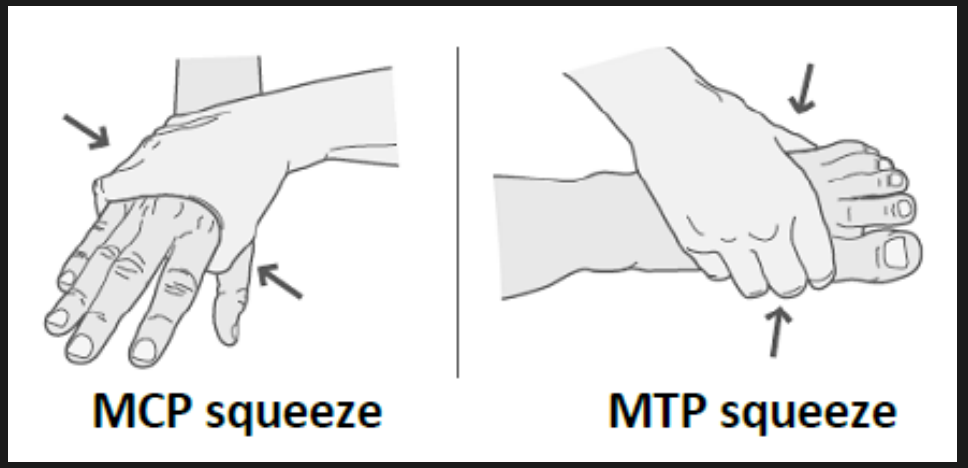
- ***In Short – Rarely***
- Theme of the day:

  *** NOT SCREENING TESTS ***

- In nearly all clinical settings serology is confirmatory to index of suspicion of disease rather than diagnostic by its own right
- In most clinical settings non-serology play a greater role in acuity of care than any of the labs do (i.e. RF vs K)

Inflammatory Arthritis

- What Constitutes Features of Inflammatory Arthritis?
  - Prolonged Morning Stiffness
  - Swelling or Tenderness of Joints
  - Abrupt or Unexpected loss of function……



Inflammatory Arthritis – Serologic Workup

- Rheumatoid Factor
- Cyclic Citrullinated Peptide (CCP) Antibody
- 14.3.3 eta Protein (?)
- Antinuclear Antibody (ANA)
- Uric Acid
- Erythrocyte Sedimentation Rate (ESR)
- C-reactive Protein (CRP)

- *<u>Other things based on clinical setting:</u>*
  - *ACE Levels*
  - *ANCA*
  - *HBsAg*
  - *HCV Antibodies*
  - *Cryoglobulins*
  - *Other ANAs*
  - *CBC*
  - *CMP*
  - *Urinalysis*
  - *SPEP*

Erythrocyte sedimentation rate (ESR)

- The “pulse” of a Rheumatologist or our Achilles Heel???
- Was originally developed as a marker to follow pregnancy
- Tested in a vertically aligned tube of anticoagulated blood and measured by distance RBCs fall over time
- Age and Gender play a role in test reliability in addition to comorbidities
  - Typical rule of thumb for adjustment[1]
    - Men: age / 2
    - Women: age+10 / 2

1: BMJ 1983;286:266

Erythrocyte sedimentation rate (ESR)

Falsely increases it

- Inflammatory disorders
- Hypergammaglobulinemia
- Hypoalbuminemia
- Tissue Necrosis
- Pregnancy
- Anemia
- Age
- Heparinized Blood
- Cold Agglutinins
- Morbid Obesity

Falsely decreases it

- Increased plasma viscosity
- Increased number of RBCs
- Change in shape of RBCs
- Decreased plasma proteins

C-reactive protein (CRP)

- Member of the pentraxin family of proteins
- It is an acute phase reactant produced by the liver under the influence of IL-6 & IL-1
- Useful as it is very acute
  - Increases within 6 hours of stimulus
  - Peaks within 50 hours
  - Falls rapidly after removal of stimulus (T1/2 = 8 hours)

C-reactive protein (CRP)

- A decompensated liver can impair production of CRP as this marker is synthesized in the liver
- Age and Gender adjustment[2]
  - Men: Upper limit of normal CRP (mg/L) = age / 50
  - Women: Upper limit of normal CRP (mg/L) = age / 50 + 0.6 (AA♀ + 1.0)

2: J. Rheum. 2000;27:2351-9

ESR / CRP – Summary

- Acute phase reactants → potential for false positive results are significant
- Most practical use is for confirmation of inflammatory disease or monitoring inflammation is some clinical settings
- Tests are less reliable as measures of rheumatic disease activity as not specific enough to illness and affected by comorbidities
  - Exceptions:
    - Systemic Vasculitis
    - Giant Cell Arteritis
      - As high as 90-100% sensitive for activity

Likelihood of Rheumatic Disease with Abnormal Labs

	RF	ANA	HLA-B27	> Uric Acid
Suspected Disease	RA	SLE	AS	Gout
Patients with positive test (%)	80	99	90	80
Prevalence positive test in normal individuals	2/100	1/100	6/100	5/100
Disease Prevalence	1/100	1/2000	1/300	1/200
Likelihood of disease if test is positive	1/2	1/20	1/18	1/10
Likelihood of disease if test positive and joint pain	1/1.5	1/5	1/4.8 1/3 (LBP)	1/2.5

Rheumatoid Factor

- What is a RF?
  - Auto-antibody directed against the Fc portion of an IgG
  - Can be of any isotype but IgG / IgM are routinely tested (some do IgA)
  - IgM is the most common
- How accurate is it?
  - Sensitivity: 60-80%
  - Specificity: as high as 78%
  - Healthy adults with a 5% incidence (>20% in those over 65 years of age)

Rheumatoid Factor

- Overall present in 70-85% of cases of Rheumatoid Arthritis
  - Incidence of disease increases with titer
- Frequency of positives increases with age in normal individuals
  - 20-60 years 2-4%
  - 60-70 years 5-10%
  - >70 years 10-25%

Rheumatoid Factor - Associations

- Rheumatic Conditions
  - RA (50-85%)
  - SLE (15-35%)
  - Sjögrens Syndrome (up to 95%)
  - MCTD (30-60%)
  - Cryoglobulinemia (up to 100% if HCV+)
  - Myositis (5-10%)
  - Sarcoidosis (15%)
  - Systemic Sclerosis (20-30%)
  - Ankylosing Spondylitis (5-10%)
  - Psoriatic Arthritis (5-10%)
- Non-rheumatic Conditions
  - HBV
  - HCV
  - HIV
  - SBE
  - TB
  - IPF
  - PBC
  - Crohn’s Disease
  - IgA Nephropathy (~25%)

Rheumatoid Factor – Associations…….

- Felty's (>95%)
- Hepatitis A
- Infectious Mononucleosis
- JIA
- Syphilis
- Influenza (A&B)
- Leukemia
- Lymphoma
- Gout (*yep that's right as many as 10%?!?!*)
- Leprosy (*as high as 50%!!!)*
- *Osteoarthritis (5-10%)*
- *Rheumatic Fever (5-10%)*
- Polyarteritis Nodosa
- ANCA Associated Vasculitis
- Viral illnesses….
- Hosts of other malignancies…..

Rheumatoid Factor – Why is it Important?

- Helpful in confirming diagnosis
- Helps to identify subgroups of patients with rheumatic disease
- Can help predict therapeutic response to therapies
- Greater titers can be prognostic indicating more severe and persistent disease
- IgA RF are more tightly associated with rheumatoid vasculitis or erosive disease
- <u>Where they can't help:</u>
  - Not helpful in monitoring disease activity in RA
  - No indicative of a treatment response in RA

*** *Outside of SBE cases RF is ordered diagnostically and nearly never followed*

Anti-cyclic Citrullinated Peptide (CCP) Antibodies

- What are they?
  - An antibody to filaggrin that has undergone post-translational modification of the amino acid arginine to citrulline
  - These peptides on fillaggrin (present in epidermal matrix) are recognized in early RA patients
- So CCP has gotta be better right?
  - Sensitivity : 33-67%
  - Specificity: 95%
- What else are they reported in?
  - Lupus, HCV, Psoriasis, Graves, Sjögrens, Tuberculosis

CCPs and their importance

- Can be diagnostic in “RF negative” RA
- Are often present in early RA and can predate development of RFs
- Can antedate synovitis in RA well prior to clinical onset of RA helping treat polyarthralgia patients earlier
- Better predictor of erosive disease than RFs
  - (+) CCP and IgM RF is most likely patient for radiographic progression
- <u>Where are they not helpful:</u>
  - Monitoring disease activity (once positive always positive)
  - Correlate poorly with potential for extra-articular manifestations (unlike RF)

14.3.3 eta Protein

- An isoform of the 14-3-3 family of intracellular chaperonin proteins
  - Chaperonins are molecular chaperones that assist in protein folding powered by ATP
- Sensitivity 77% and Specificity 93%
  - Very similar to citrullinated peptide antibodies
- Has been associated with worse disease
- In a few cohort study looking at polyarthralgia patients adding it to workup did not increase likelihood of diagnosis of RA
- Assay is currently readily available
  - further study is needed to justify a role for the assay in routine clinical practice

The Dreadful Antinuclear Antibody

- The “Lupus Test” that more often means something other than Lupus
- An antibody directed against nuclear antigens screened for best by indirect immunofluorescence using hep-2 cells as a substrate
- The nuclear antigenic target determines the “sub”-antibody
  - Following up testing (i.e. anti-dsDNA and other ENA)
- Methodology ***greatly*** affects false (+) and false (-) rates
- Seen in 5-30% of normal individuals and affected significantly by age
  - ≥ 1:40 20-30% *(some studies above 50% in those over 65)*
  - ≥ 1:80 10-12%
  - ≥ 1:160 5%
  - ≥ 1:320 3%

Conditions Commonly Associated with ANAs

- Rheumatic Diseases
  - SLE
  - Polymyositis
  - Sjögren Syndrome
  - Scleroderma
  - Vasculitis
  - Rheumatoid Arthritis
- Normal Health Individuals
  - Elderly
  - Women (especially pregnant)
- Hematologic Disorders
  - AIHA
  - ITP
- Hepatic Diseases
  - Chronic Active Hepatitis
  - Primary Biliary Cirrhosis
  - Alcoholic Liver Disease
- Malignancies
  - Lymphoma
  - Leukemia
  - Melanoma
  - Solid Tumors
- Pulmonary Diseases
  - IPF
  - Asbestosis-induced Fibrosis
  - Primary Pulmonary HTN

****Also noted in Hashimotos, Graves, DM, MS, ESRD and organ transplantation patients*

Drugs Associated With Production of ANAs

- PAS
- Tegretol
- Thorazine
- Zarontin
- Apresoline
- Isoniazid
- Mesantoin
- Aldomet
- Metformin
- Sulfonylureas
- Statins
- Dilantin (and derivatives)
- Beta Blockers
- PTU
- Mysoline
- Procainamide
- Trimethadine
- Thiazides
- Tetracylines
- Oral Contraceptives

Infections Associated With Production of ANAs

- HBV
- HCV
- HIV
- Mononucleosis
- SBE
- Tuberculosis
- Lyme Disease
- Rickettsial infections
- Parasitic infections

- And the list goes on,
  - and on,
  - and on,
  - and……..

Antinuclear Antibody Sensitivity

Disease	% with Positive ANAs
Systemic Lupus Erythematosus	99%
Drug Induced Lupus	100%
Mixed Connective Tissue Disease	93%
Sjögren Syndrome	48%
Systemic Sclerosis	85%
CREST Syndrome	45%
Polymyositis / Dermatomyositis	61%
Rheumatoid Arthritis	41%

Sensitivity ≠ Specificity

	dsDNA	RNP	Smith	SSA	SSB	Cent
SLE	60%	30-45%	30%	30%	15%	Rare
RA	(-)	(-)	(-)	Rare	Rare	(-)
MCTD	(-)	>95%	(-)	Rare	Rare	Rare
PSS	(-)	>95%	(-)	Rare	Rare	10-15%
CREST	(-)	(-)	(-)	(-)	(-)	60-90%
SjS	(-)	rare	(-)	70%	60%	(-)

Significance of Pattern

Pattern	Nature of Antigens	Function of Antigens	Autoantibody	Associated Disease
Homogenous / Diffuse	Histone Classes (i.e. H1 H2A…)	Linkage of nucleosomal DNA	Histone	SLE, DIL
Rim / Peripheral / Shaggy	Double or Single stranded DNA	DNA replication and repair	dsDNA	SLE
Speckled	Proteins A-G, snRNAs, U1-6, Nucleoproteins	Splicing of pre-mRNA, processing RNA polymerase	ENA – RNP & Smith SS-A, SS-B	SLE, MCTD, Sjogrens
Centromere	Kinetochore	Cell division	Centromere	CREST
Nucleolar	nRNA	Transcription promotion	Jo-1	Myositis

ANA Profiles in ANA-Positive Rheumatic Disease

Antibody Specificity	ACTIVE SLE	MCTD	PSS	CREST	PRIMARY SJOGRENS	RA	DIL
ANA	>95%	>95%	70-90%	60-90%	>70%	40-50%	100%
Anti-ds-DNA	60%	Negative	Negative	Negative	Rare	Rare	Negative
Anti-Sm	30%	Negative	Negative	Negative	Negative	Negative	Negative
Anti-RNP	30%	>95% (high titer)	Common (low titer)	Negative	Rare (low titer)	Rare	10-20% (low titer)
Anti-Centromere	Rare	Rare	10-15%	60-90%	Negative	Negative	Negative
Anti-Ro (SSA)	30%	Rare	Rare	Negative	70%	10-15%	Negative
Anti-La (SSB)	15%	Rare	Rare	Negative	60%	Rare	Negative
Anti-Nucleolar	Occasional	Negative	Common	Negative	Occasional	Rare	Negative
Anti-Scl-70	Rare	Negative	10-20%	Negative	Negative	Negative	Negative
Anti-Histone	24-95%	Occasional	Occasional	Occasional	Occasional	20%	Procainamide: 60-70% Sensitivity Hydralazine: 50-100% Sensitivity
Anti-	70%	Occasional	Occasional	Occasional	Occasional	Occasional	Procainamide: >90% Sensitivity

ANAs – take homes

- They represent a diverse group of autoantibodies reacting to intranuclear, intranucleolar or intracytoplasmic antigens
- They are an unreliable definitive diagnostic test
  - Have a suspicion for underlying CTD and order specific ANAs accordingly but don't be discouraged by a negative result if index of suspicion remains high
- Size Does Matter!!!! (*Watch for the significance of titer and pattern)*
- Always think of alternate non-rheumatic causes if clinical picture does not fit
- Titer of antibody rarely correlates to severity of disease or response to treatment
  - *Exceptions: dsDNA and C'*
- The clinically relevant internal manifestation of disease always matters more than the ANA

Myopathies

- Myalgia ≠ Myopathy
  - Must clinically separate muscle pain from weakness
  - Both have a host of causes: Neuropathic, Inflammatory, Infectious, Toxic…….
- >50% of patient > 50 with a ESR over 50 have polymyalgia
  - Those with signs of TA with highly elevated ESR very likely have GCA (90%)
- Creatine Kinase
  - Elevations are not really specific for any particular disorder
  - The more elevated it is the more likely a myopathy is present
  - Elevations in autoantibodies or acute phase reactants in addition can help narrow cause

Creatine Kinase Normals

- Most labs have a CK 0-200 as the reference range
  - At this level 5% of women and up to 20% of males will have increased baseline levels
- Not only gender but race plays a role in baseline levels
- One analysis looking to establish the 97.5th percentile for serum CK
  - Caucasian Females 217
  - Caucasian Male 336
  - African American Male 414
  - African American Female 801

Brewster et al 2007

Myopathies - Inflammatory

- There are many antibodies that occur exclusively in patients with myositis
- Occur mainly in two groups:
  - Anti-nuclear Antibodies*****
  - Anti-cytoplasmic antibodies
    - Anti-synthetase antibodies (anti-Jo-1, anti-PL-7, anti-PL-12, anti-OJ & anti-EJ)
    - Non-synthetase antibodies (anti-SRP)
- Clinical syndromes are important and associated with myositis such as malignancy
  - Dermatomyositis >> Polymyositis

Antibody	Myositis Specific	Myositis Associated	PM	DM	Anti-synthetase Syndrome	Overlap Syndrome	Juvenile Myositis	ILD	Arthritis
Mi-2	4 – 14%	Not Applicable	Rare	Common	Not Applicable	Common	10%	Rare	Occasional
SRP	4%	Not Applicable	Common	Occasional	Not Applicable	Not Described	Uncommon	Common	Common
Jo-1	20%	Not Applicable	Common	Occasional	Marker	Common	Reported	Common	Common
PL-7	1 – 4%	Not Applicable	Occasional	Common	Marker	Common	Reported	Common	Common
PL-12	1 – 4%	Not Applicable	Occasional	Common	Marker	Common	Reported	Common	Common
OJ	1 – 4%	Not Applicable	Occasional	Common	Marker	Common	Reported	Common	Common
EJ	1 – 4%	Not Applicable	Occasional	Common	Marker	Common	Reported	Common	Common
PM/Scl	Not Applicable	8%	Uncommon	Uncommon	Not Applicable	Common (~25%)	Occasional	Rare	Common
Ku	Not Applicable	% Unknown	Not Described	Not Described	Not Applicable	Common	Occasional	Not Described	% Unknown
U2 snRNP	Not Applicable	% Unknown	Not Described	Not Described	Not Applicable	Common	Not Described	Not Described	% Unknown

HMGCR Antibody Associated Myopathies

- In the past decade reports of chronic myopathies after statin use have been noted
- In 2010 antibody discovered that was IgG binding to 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) in patients with presumed immune myopathies that usually have no lymphocytic cell foci[3] that were termed HMGCR Antibodies
- Distinct clinical entity of necrotizing myopathies that damage perimysial connective tissues and muscle fibers
- Reference ranges were established and test available but not done routinely in practice yet → likely coming when clinical algorithm can be established
  - False positive rate with this antibody shocking low for this necrotizing myopathy
  - Antibody does not seem to be present in other forms of immune based myopathies
  - Up to 30% Anti-HMGCR positive patients have not been exposed to statins

3: Christopher-Stine L, Hong G, Chung T, Mammen AL. Arthritis Rhem 2010;62:2757-2766

Myositis – Take Homes

- Know what you are working up – Myalgia or Myopathy
- Underlying cause can affect labs – toxic vs inflammatory vs other
- Creatine Kinase
  - If not clinically impressive ponder if value could be baseline for patient
  - Eliminate other causes when minimal or no clinical symptoms found
  - Be wary of patients with cardiopulmonary symptoms or dysphagia as these patients require urgent referral***
  - As you “build” abnormal labs likelihood of disease increases
    - Elevated CK, abnormal ESR, Elevated LAEs, Abnormal ANA……..

Scleroderma

- Most common antibody is simply an ANA
  - Typically Nucleolar pattern (scl-70 antibodies are uncommon)
- Other antibodies occur infrequently but when present have clinical importance
  - They can help to guide therapy
  - They are useful in helping direct monitoring of patients
- Higher the titer of specific antibody the greater concern for associated clinical illness
  - Not having the particular antibody ***does not*** exclude the illness or complication
- Important to know patterns of disease in relevance to serology to assess risk and follow patients most appropriately

Scleroderma Autoantibodies

Autoantibody	Prevalence	Clinical Syndromes	Associated Clinical Features
Anti-Nuclear Antibody	Extremely High	*Nucleolar pattern suggests RNA-polymerase III, Anti-PM/Scl, Anti-Th/To & Antifibrillarin (15-40%)*	
Anti-Scl-70 (Anti-Topoisomerase 1)	20%	Highly specific for diffuse cutaneous SSc	Increased frequency in pulmonary fibrosis Increased mortality rate Renal involvement not uncommon
Anti-RNA Polymerase III	20%	Highly specific for diffuse cutaneous SSc SSc related renal crisis	Greater overall mortality rate
Anti-Centromere	20 – 30%	Limited SSc/CREST Variant	Increased risk pulmonary hypertension Lower frequency of pulmonary fibrosis Raynauds Phenomenon predominant Higher risk of calcinosis and ischemic digital loss More prevalent in Caucasian ethnicity
Anti-Th/To	2 – 5%	SSc with milder skin and systemic involvement	Severe pulmonary fibrosis (poor prognosis) Pulmonary Hypertension
Anti-U1 RNP	8%	SSc with less cutaneous and renal involvement	Mixed Connective Tissue Disease (strong positive) Pulmonary disease and pulmonary hypertension Esophageal Disease
Anti-Fibrillarin (U3 RNP)	< 10%	Diffuse Cutaneous SSc	Renal Disease Associated with myositis Pulmonary Hypertension More prevalent in African-American ethnicity
Anti-PM/Scl	2% 24%	SSc with limited skin disease Polymyositis-SSc overlap syndromes	Arthritis More prevalent in African-American ethnicity

Human Leukocyte Antigen B27 (HLA-B27)

- Class I surface antigen encoded by the B locus in the Major Histocompatibility Complex (MHC) on chromosome 6 and presents antigenic peptides to T cells
- Seen in 85-95% of Caucasian patients with AS yet their presence in a patient is not diagnostic of spondyloarthropathy
  - Sensitivity changes based on race,
  - Marker present in 8% of the general population
    - Estimated that around 10% of individuals with this gene will develop spondyloarthritis
  - Associated with a variety of diseases like ankylosing spondylitis, psoriasis, inflammatory bowel disease, reactive arthritis among other entities
- Positive result does not absolutely confirm or exclude spondyloarthropathy
  - About 10-20% of patients with AS will test negative – sensitivity worse for other subtypes

Uric Acid

- This is only a diagnostic test for hyperuricemia ***NOT*** Gout
- 2007 US Census Statistics
  - 228 Million - US Adult Population[4] – ~43 Million Hyperuricemic[5] – ~6 Million Gout[6]
- Many medications, disease states (e.g. psoriasis) or comorbidities affect level
- Gold standard for diagnosis of gout is still arthrocentesis for MSUM crystals
- Timing of test plays a role in finding hyperuricemia in Gout patients
  - Serum uric acid baseline may decrease by as much as 50% during flare[6]

4:US Census Statistics 2009 5:NHANES III 1994 6: Urano W, et al. *J Rheumatol.* 2002;29:1950-1953

Uric Acid

- Patients with established Gout not treated to a target sUA <6
  - Are still symptomatic
  - Have ongoing joint damage even during asymptomatic periods
  - Continue to develop tophaceous deposits
- KEYS TO REMEMBER:
  - Likelihood of Gout in hyperuricemic patient ~1/10
  - Likelihood of Gout in hyperuricemic patient with joint pain ~1/2.5
  - sUA can be used as a target for treatment with Gout with a goal of < 6 mg/dL
    - Some evidence women should have a lower target
    - Patients with tophaceous deposits or severe disease should be targeted < 5mg/dL[7]

7: Rheumatology, Volume 57, Issue suppl_1, 1 January 2018, Pages i20–i26

Vasculitis Workup

Workup and differential has always been driven by size of affected blood vessel involved

- Large
  - Takayasu's arteritis
  - Giant Cell Arteritis
- Medium
  - Polyarteritis Nodosa
  - Kawasaki's Disease
  - Central Angiitis / Isolated CNS Vasculitis
- Small
  - Immune Complex Associated
    - Hypersensitivity vasculitis
    - Cryoglobulinemic vasculitis
    - Henoch-Schönlein purpura
  - Pauci Immune Associated
    - Granulomatosis with Polyangiitis
    - Microscopic Polyangiitis
    - Churg-Strauss vasculitis
  - Malignancy Associated
  - CTD related
  - Mimics

What Lab Tests are Useful in Evaluation?

- Tests for Systemic Inflammation
  - CBC – anemia, thrombocytosis, eosinophilia
  - ESR – usually >100 mmHg in absence of infection
  - CRP - usually >10mg/dL in absence of infection
  - Low Albumin – “negative acute phase reactant”
- Tests for Organ Involvement
  - Creatinine and Urinalysis
  - LAEs
  - Creatine Kinase
  - Stool for occult blood
  - Chest radiographs
  - Abdominal CTA or conventional angiogram
  - Brain MRI / MRA

What Should Be Done for Initial Lab Workup?

- CBC, CMP, CK and Urinalysis with microscopic analysis to screen for extent
- RF – Endocarditis first then Rheumatoid Vasculitis in long standing RA but most commonly this is a marker cryoglobulins will be positive
- ANA – think SLE but could be Sjögrens among many others
- Cryoglobulins
- HBV and HCV
- CH50 C3 C4
- C-ANCA and P-ANCA
- Blood Cultures
- SPEP

What Lab Tests are Useful in Evaluation?

- Tests suggesting ANCA associated vasculitis
  - C-ANCA (PR3) – most likely GPA less likely MPA
  - P-ANCA (MPO) – consider MPA and CSS (and possibly anything else – IBD, infections)
- Tests suggesting etiology
  - Blood Cultures – helps to rule out SBE
  - Infectious Serologies – helps to suggest: HBsAg (PAN-25%), HCV (Cryoglobulinemia, PAN-rare), parvovirus IgM (GPA, PAN), Herpes CMV and HIV (any vasculitis)
  - SPEP – helps to rule out multiple myeloma
  - CSF Studies – helps to rule out herpes and varicella-zoster

Clinical Utility of ANCA

- What are they?
  - Antibodies directed against components of granules in the cytoplasm of neutrophils
    - Patterns noted in:
      - cytoplasm (C-ANCA) → commonly associated with proteinase 3 antibodies
      - peri-nuclear (P-ANCA) → commonly associated with myeloperoxidase antibodies
      - Atypical peri-nuclear → seen in Ulcerative Colitis patients frequently
- Doesn’t every ANCA Associated Vasculitis patient have a (+) ANCA?

Clinical Utility of ANCA

- C-ANCA / PR3 Ab
  - Present in ~90% in GPA
  - Sensitivity decreases to 60% in limited disease
  - Titers rarely useful in monitoring activity of disease
- P-ANCA / MPO Ab
  - ~90% ANCA associated GN, ~75% of MPA, 75% EGPA
  - False positives very common in SLE, UC, PBC, PSC, AIH, Goodpastures, RA, Myositis, Sjögrens
- Drug induced ANCAs common
  - PTU, minocycline, hydralazine are testworthy but list is *LONG*
- Infections also associated
  - SBE, Cystic Fibrosis, HIV, HCV, HBV, Acute Malaria

ANCA Frequencies in Antibiotics

Disease Category	C-ANCA	P-ANCA	ANTI-MPO	ANTI-PR3
Granulomatosis with Polyangiitis (GPA) Active – generalized Active – limited	3-4+ 2-3+	1+ Occasionally	1+ <1+	3-4+ 2-3+
Idiopathic Necrotizing and Crescentic Glomerulonephritis without Immune Deposits (Pauci-Immune)	Rare	4+	3-4+	Rare
Microscopic Polyangiitis (MPA)	1+	2-3+	2-3+	1+
Eosinophilic Granulomatosis with Polyangiitis (EGPA)	1+	2+	2+	1+
Classic Polyarteritis Nodosa Polyangiitis Overlap Syndrome	Rare 1+	Rare 1+	Rare 1+	Rare Rare
Inflammatory Bowel Disease Ulcerative Colitis Crohn’s Disease	 Absent Absent	 2-4+ 1+	 Absent Absent	 Absent Absent

Grading System: 1+ (15-25%); 2+ (26-50%); 3+ (51-75%); 4+ (76-100%)

Summary

- Rheumatology Labs are more often less diagnostic than they are confirmatory
- Frequently our “base workup” is more reliable in suggesting severity of disease
  - Titers are less frequently as significant as organ involvement
- Trust your clinical impressions independent of labs
  - The hypertensive young woman with skin thickening and raynaud’s that can’t complete a sentence talking to you is an emergency even if the ANA is negative and ESR in normal
- Know when that labs do matter
  - Elevated ESR with temporal headaches and jaw claudication in GCA
  - Petechial rashes with organ dysfunction
  - dsDNA with chronic hematuria and a mild increase in renal function

Q&A

1) What constitutes a significant ANA?
   - Symptoms of connective tissue disease not attributable to other causes in association with the ANA. (significant titer 1:160)
2) How predictive is a positive rheumatoid factor in diagnosing Rheumatoid Arthritis?
   - Sensitivity is about 2/3 of cases. As titer increases it becomes more likely associated with disease. Likelihood of disease additionally increases if associated with other autoantibodies.
3) What positive results could indicate a need for more urgent referral?
   - Elevated ESR/CRP with GCA features, elevated ESR/CRP with signs of vasculitis and any organ dysfunction, elevated CKs with cardiopulmonary or gastrointestinal involvement, Abnormal dsDNA and hematuria, patients with (+) ANA and low C’ or any organ dysfunction, RF/CCP with severe debility or any systemic features.