Rheumatologic Testing: What Do I Order?

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Disclosures

- Positions: University of Manitoba, WRHA
- Advisory Boards: Janssen, Pfizer, Novartis, Eli Lilly, UCB
- Speaking Honoraria: Janssen, Pfizer

- Mitigated by the fact that no treatment will be discussed today

Objectives

- At the end of this presentation, you will be able to:
  - Understand the indications for ordering rheumatologic testing
  - Know which tests to order for which clinical presentations
  - Know when to refer to a rheumatologist

Outline

- ANA
- RF/CCP
- MPO, PR3, and ANCAs
- Antiphospholipid antibodies
- HLA-B27
- What Do I Order?
- When To Refer

Notes

- Any of the comments here refer to the adult population only

ANA

The Dreaded ANA…

- What exactly is this test?
- Why do I sometimes get a result that just says “positive” and sometimes get a result that gives a titre (e.g., 1:80)?
  - Because there are TWO ANA tests! (Just to keep it confusing)

The Dreaded ANA…

- The original ANA (HEp2 on the req) is an indirect immunofluorescence test
  - This is the one that gives you a titre
  - Very subjective test ("positivity" at any given serum dilution is judged by a tech viewing the slide under a UV microscope)
  - More sensitive
- ANA screen is a totally different test!
  - ELISA-based assay of 11 specific antibodies
  - Any one of these antibodies being positive triggers a "positive" report for the ANA itself
  - Less sensitive

The Dreaded ANA…

- Exciting (to me) changes coming:
  - Soon positive ANAs will get reflex reporting of the specificities!
  - Will be switching from ELISA assay to line immunoassay (except dsDNA)
  - Meaning: No more of me having to send patients for repeat blood draws to find out what's driving the positive ANA

ANA Patterns- what do they mean?

- IF patterns tend to correlate with certain specificities on the ANA screen
- Homogenous: dsDNA, histone, chromatin
- Speckled: Ro, La, Smith, RNP
- Nucleolar: Scl-70, Pm/Scl, Th, RNA pol 3, others
  - This one for me is the scary one!
- Centromere: centromere (…)
- Many others

Diseases Associations

- Ro and La: Sjogren’s, lupus, RA, sometimes others
  - Neonatal lupus
- dsDNA: lupus (specifically lupus nephritis)
- Smith: lupus (very specific!)
- Ribosomal P: lupus (specifically neuropsychiatric lupus)
- RNP: mixed connective tissue disease (a diagnosis that has features of RA, SLE, PM, and SSc)
- Centromere and Scl-70: scleroderma
- Jo1: anti-synthetase syndrome (a subtype of dermatomyositis)
- Chromatin: very nonspecific
- There are many more specific autoantibodies that can be tested for at labs outside Manitoba (e.g., Mitogen Laboratories in Calgary)

When To Order an ANA

- If you are suspicious a patient has lupus, scleroderma, or other specific connective tissue disease
- Young women or other high risk groups with inflammatory arthritis
- When patient has one disease manifestation that could be autoimmune (e.g., new diagnosis of ILD)

When NOT To Order an ANA

- Vague nonspecific pain/fibromyalgia
- Low back pain
- For general screening (10-20% of population is positive[1] so not helpful for screening purposes in this way)

[1]Tan et al., Arthritis Rheum, 1997

RF and CCP

Rheumatoid Factor

- What is it?
  - IgM targeting IgG (an antibody to an antibody)
- Anything causing chronic immune stimulation can cause a positive RF
  - Subacute bacterial endocarditis
  - Chronic viral hepatitis
  - Malignancy (especially B cell lymphomas)
  - Others
- ~5% of normal population is RF positive[1]

[1]Nielsen et al., BMJ, 2012

When To Order an RF

- If you think someone has inflammatory arthritis
- NOT a screening test for vague pain
- NOT a test for back pain
- PLEASE order CCP with the RF (much more specific for RA than the RF is)

CCP Antibody

- Anti-cyclic citrullinated peptide antibody
- One of many anti-citrullinated peptide antibodies that can be seen in RA (collectively called ACPAs)
- More specific for RA than RF, equally as sensitive
  - 50% risk of developing inflammatory arthritis within next 12 months[1]
  - Infrequently positive in the healthy population (0.8%)[2]

[1] Nam et al., Ann Rheum Dis, 2016
[2] Zanten et al., Ann Rheum Dis, 2017

Antiphospholipid Antibodies

Antiphospholipid Antibodies

- Anti-cardiolipin (IgM and IgG)
- Anti-B2-glycoprotein (IgM and IgG)
- Lupus inhibitor (aka lupus anticoagulant)- reported as a ratio in MB using dRVVT

Okay… what are these tests?

- Despite the name, lupus inhibitor is not a test for lupus!
- Used to diagnose antiphospholipid syndrome
  - Checked in cases of suspicious blood clotting (venous or arterial)
  - OR in patients meeting clinical criteria for obstetric APLS
- Sometimes I will screen patients without a clot history for these antibodies (lupus, livedo reticular, etc)
  - Probably no need to use these tests for screening purposes in primary care

Antiphospholipid Antibodies

- Remember: In order to consider them significant, they need to be persistently positive (two positives at least 12 weeks apart)
- False one-time positives are common:
  - Bacterial/viral infections, malaria, PJP
  - Medications (hydralazine, phenytoin, OCPs, propranolol, etc
  - Malignancy (solid organ, hematologic)

Vasculitis Antibodies

Vasculitis Antibodies

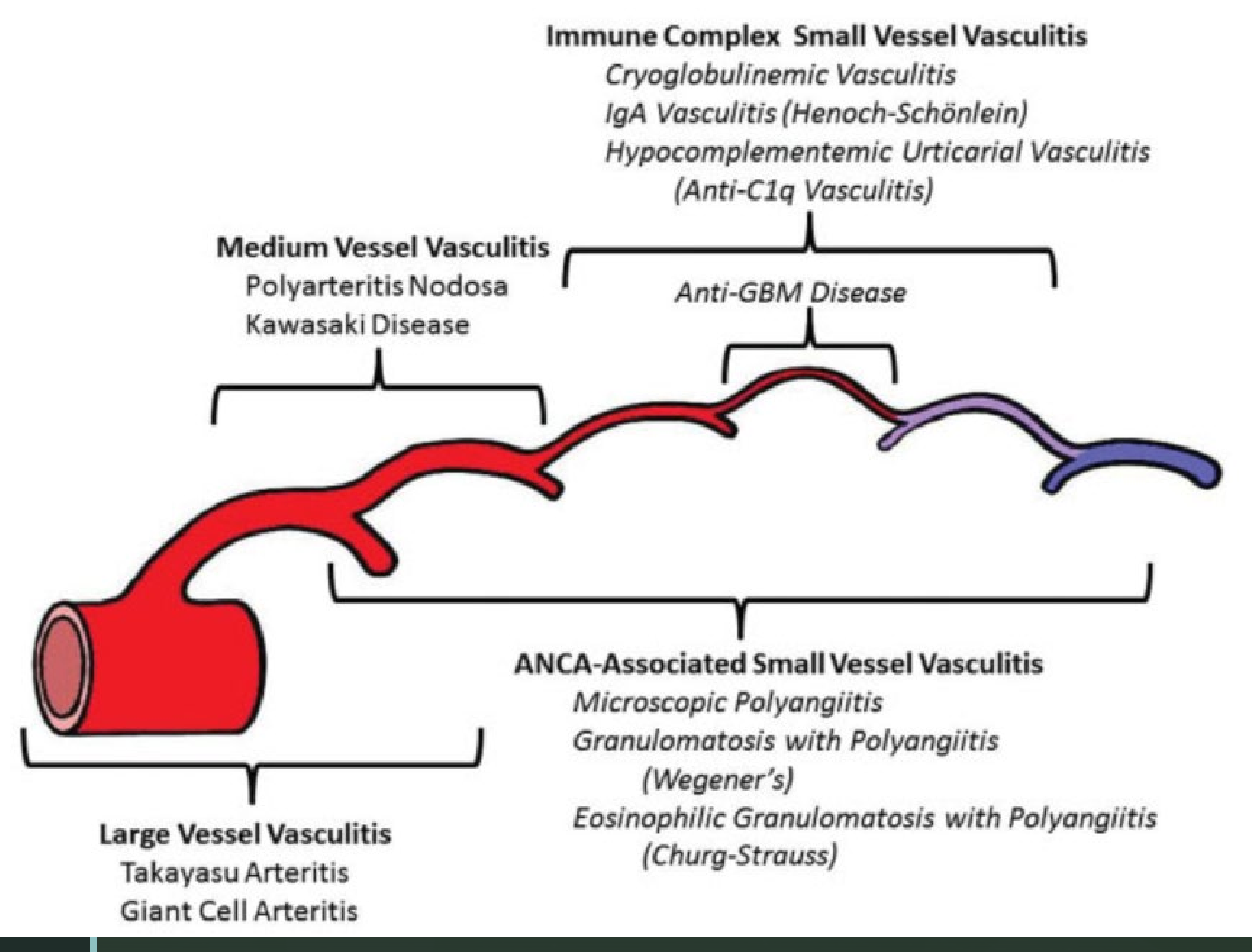
- Unfortunately, to understand the antibodies, I have to teach you a little about vasculitis nomenclature… (sorry)

A Large Vessels

B Medium Vessels

C Small Vessels

Jennette et al., Arthritis & Rheumatism, 2013



Not pictured:

-Variable vessel vasculitis (Behcet's, Cogan syndrome)

-CTD-associated vasculitis (e.g., lupus vasculitis, rheumatoid vasculitis)

-Vasculitis with a probable etiology (e.g., HBV, drug-induced)

Jennette et al., Arthritis & Rheumatism, 2013

Vasculitis Antibodies

- ANCAs (anti-neutrophil cytoplasmic antibodies)
  - Immunofluorescence test (cytoplasmic equivalent of ANA)
  - More sensitive, less specific
  - Reported as pANCA, cANCA, or atypical patterns
    - pANCA has a low specificity for vasculitis
    - Atypical is very nonspecific
- MPO and PR3
  - ELISA for specific antibodies that can cause positive ANCAs
  - Anti-MPO antibodies are one cause of positive pANCA
  - Anti-PR3 antibodies are one cause of positive cANCA
  - Overall much more specific for vasculitis than ANCA by IF

Vasculitis Antibodies

- MPO/PR3 only seen in small vessel vasculitis
- MPO: associated with microscopic polyangiitis
- PR3: associated with granulomatosis with polyangiitis
- Not hard-and-fast rules
    - Also does not really matter, treatment is largely the same for MPA and GPA

Vasculitis Antibodies

- So what antibodies do we test in suspected medium/large/variable vessel vasculitis?
- None! There are no testable antibodies associated with these diseases
- Instead: Need vascular imaging or a biopsy to prove vasculitis is present

HLA-B27

HLA-B27

- Genetic test that identifies whether patient is a carrier of the B27 allele
- This allele may have a direct pathogenic role in the development of ankylosing spondylitis
- Up to 90% of ankylosing spondylitis patients are B27 positive
  - *Somewhat lower rates in non-Caucasian populations
- Other spondyloarthridities are less strongly associated with B27

HLA-B27

- Up to 10-20% of the population is B27 positive[1]
  - Much more common in those of European and Indigenous ancestry
- However, only 2% of carriers ever develop AS[2]
  - Rate goes up to 20% if first degree relative with AS

[1]Sheehan, J R Soc Med, 2004
[2]Robinson et al., Rheum Dis Clin N Am, 2012

What Not To Do

- DON'T use antibody testing as screening for vague complaints
- DON'T order autoantibodies for low back pain
- DON'T repeat autoantibodies to see if the levels are changing or if they have become positive to explain a chronic symptom
  - If autoantibodies are going to develop, they show up in blood years prior to the onset of clinical autoimmune disease[1]
  - Generally, no role for monitoring titres (with some exceptions)

[1]Arbuckle et al., N Eng J Med, 2003

What Do I Order?

- New inflammatory arthritis:
  - CBC, Cr, liver enzymes (baseline for starting DMARDs)
  - ESR, CRP (may or may not be elevated; helpful for monitoring if high)
  - RF, CCP
  - Xrays of hands/feet (for baseline) +/- L spine and SI joints
  - Maybe: CTD workup (next slide), urate, CXR to r/o sarcoid, urine G&C, Lyme serology, hepatitis/HIV/syphilis serology, SPEP

What Do I Order?

- Suspected connective tissue disease (lupus, scleroderma, etc):
  - ANA screen with all specificities
  - ANA by HEp2 (yes, I want both)
  - C3/C4
  - CBC with differential (need to see ALC), Cr, liver enzymes, UA, urine PCR, ESR, CRP
  - Maybe: CK, myoglobin, APLAbs (if I think they have lupus)

What Do I Order?

- Suspected vasculitis:
  - CBC, Cr, liver enzymes, UA, urine PCR
  - CXR (lung involvement) or CT chest
  - MPO, PR3
  - ANA, C3/C4
  - Cryoglobulins
  - Hepatitis/HIV serology
  - Biopsy if at all possible*
    - *Some disease manifestations are not helpful to biopsy, e.g., nasal mucosa
  - Maybe: APLAbs (if looking like a medium vessel picture), vascular imaging, RF/CCP, SPEP/FLC ratio

What Do I Order?

- Inflammatory back pain:
  - XR L spine/SI joints +/- C/T spine films
  - Cr, ESR, CRP
  - HLA-B27 (maybe)
  - If XRs negative, disease duration is short (reduces sensitivity of XRs), and index of suspicion high: MRI SI joints

When To Refer To Rheumatology

- If you are legitimately concerned a patient may have inflammatory arthritis/connective tissue disease
  - Regardless of autoantibodies being positive/negative
- Specific positive autoantibodies
  - Smith, dsDNA, Jo1, RNP, centromere, Scl-70, CCP, MPO, PR3
- If you're worried about your patient and/or if you aren't sure what's going on

Questions?

- My office phone: 204-788-5722
- Can call me any time if questions/concerns about patients