“Now What?: Interpreting Rheumatologic Labs”
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Learning Objectives
- Interpret the significance of an elevated ESR and CRP
- Summarize the causes of a positive RF and anti-CCP
- Discuss the evaluation of a positive ANA
- List the diseases associated with hypocomplementemia
- Differentiate the types of ANCAs

Case: History
- 52 yo woman admitted for a 3 month history of worsening polyarthralgias, myalgias, lower extremity rash, and burning feet.
- ROS: dry mouth, hx of sinusitis x 2, no fever, cough, or weight loss
- PMH: HBP on HCTZ and lisinopril, hyperlipidemia on simvastatin, overweight, smokes 1 PPD
- PSH: Auto accident age 20 with splenectomy, transfusion; cholecystectomy age 45.
### Case: Physical Examination
- NAD, uncomfortable
- VS: Afebrile, P= 72, BP= 145/92
- HEENT: poor dentition
- CHEST: scattered rhonchi
- CVS: 1-2/6 soft systolic murmur LLSB
- ABD: overweight
- EXT: Mild puffiness and tenderness of MCPs/PIPs with tenderness wrists, knees, and MTPs
- NEURO: Decreased sensation LEs, no ankle reflexes
- SKIN: Palpable purpura

### Case: Laboratories
- CBC: Hct 35% with MCV 76, WBC 6800 nl diff, plts 432,000. Reticulocyte count 1%
- CMP: Cr 1.3, K+ 3.2, AST 65, ALT 54, albumin 3.0
- U/A: 2+ protein, 20 RBCs/ HPF, one RBC cast seen
- ESR: 54mm/hr, CRP: 3.8 mg/dL
- RF: 80 IU/ml, ANA 1:80, antiCCP: neg
- cANCA: neg; pANCA 1:16 with neg antitymepoperoxidase
- Stool for blood: negative
- CXR: bronchial wall thickening
- Hand, wrist, feet xrays: no erosions
Case: Differential Dx

- Infection: SBE, viral, other
- Neoplastic: lymphoma, paraneoplastic
- CVD: RA, SLE, Sjogren's, other
- Vasculitis: HSP, Wegener's, other
- Drug reaction: HCTZ

Skin biopsy with immunofluoresence ordered

Leukocytoclastic vasculitis with clot. No IgA deposits. Sparse IgM, C3 deposits
Interpretation: not HSP

Erythrocyte Sedimentation Rate (ESR)

Upper limit for normal sed rate: males= 15mm/hr or age/2
females= 20mm/hr or (age + 10 )/2
ESR increased by large asymmetric molecules: fibrinogen, alpha macroglobulins, and immunoglobulins
Elevated ESR

- Elevated fibrinogen
  - Elevated = 1/2 macroglobulins
  - IgG
  - Monoclonal
  - Polyclonal
  - Myeloma
  - Lymphoma
  - CTD
  - Others

Pearl: Always get SPEP and CRP in pt with unexplained high ESR

C-reactive protein

- Acute-phase protein synthesis including CRP made by liver in response to cytokines (IL-6) released by activated macrophages after tissue injury.
  - Albumin levels decrease during acute phase response
- CRP reported as mg/dL (0-1) or mg/L (0-10) depending on laboratory
- PEARL: CRP levels > 10x ULN indicate bacterial infection, systemic vasculitis, major trauma, widely metastatic cancer, or polyarticular crystal attack (gout, CPPD)

Case

- Hct 35% with MCV 76, low retics
  - Iron 28, %sat 14%, TIBC 274, Ferritin 230
  - IL-6 stimulates hepcidin that stops ferroportin from releasing iron stores causing iron sequestration in bone marrow leading to anemia of chronic disease. Patient may have low serum iron/%sat/TIBC but does not have iron deficiency if ferritin > 60-100.
- ESR: 54 mm/hr (nl 0-30)
- CRP 3.8 mg/dL (nl 0-1)
- SPEP/IEF: polyclonal gammopathy with small IgM monoclonal spike (0.1gm/L)
- Interpretation: Chronic inflammation with tissue injury. Small monoclonal spike. Anemia of chronic disease.
- Diff Dx: Lymphoma, CVD, Wegener’s, SBE
**Rheumatoid factor (RF)**

RF is an immunoglobulin that reacts with the Fc portion of IgG.

### Caveats on RF

- Different methods to detect RF: latex agglutination (significant titer >1:80), ELISA, nephelometry (> 50 IU/ml)
- A positive RF doesn’t mean the person has RA but usually associated with chronic immune stimulation
  - CTD: RA (70-85%), mixed cryoglobulinemia (80%), SLE (30%), Sjogren’s (80%), MCTD (50%), scleroderma (20%), polymyositis (10%), others
  - Nonrheumatic disease: viral (HIV, mono, hep B/C), parasitic, chronic bacterial (TB, SBE, osteo, others), lymphoproliferative, chronic liver disease (PBC), chronic pulmonary disease (ILD), sarcoidosis
- Normal individuals: 5-10% of pts > age 65. Increases with age. Low titer (<1:260, < 50 IU/ml)

**Anti-cyclic citrullinated protein (Anti-CCP)**

- Arginine residues in numerous proteins can be deiminated to form citrulline by the enzyme, peptidylarginine deiminase (PAD). This is a normal process which is accelerated at sites of local inflammation.
- Patients with rheumatoid arthritis can form antibodies to these citrullinated proteins.
- Value of anti-CCP in patients suspected to have RA
  - High sensitivity (70%), specificity (95%) for RA
  - More likely to develop erosions (10x). Maybe worse prognosis
RF and anti-CCP predictive value

- Early inflammatory arthritis
  - Elevated RF predicts evolution into RA especially at higher titers (1:640, > 50 IU/ml)
  - More likely to develop nodules/ERMs
- Anti-CCP gives odds ratio of 25x increased risk of evolving into RA
- Present ordering habits
  - PPV of positive RF is 24% for RA and 34% for any rheumatic disease
  - NPV of a negative RF is 89% that the patient doesn’t have RA and 85% that the patient does not have any rheumatic disease.

Case

- RF 80 IU/ml
- Anti-CCP negative
- Interpretation: significant RF but can’t confirm RA.
- Diff Dx: lymphoma, CVD, Wegener’s, SBE

Antinuclear antibodies (ANA)
### Caveats on ANAs

- Different methods to detect ANAs: indirect immunofluorescence (significant titer on Hep-2 cells > 1:80), ELISA
- A positive ANA does not mean a person has SLE.
  - CTD: SLE (100%), MCTD (100%), DLE (100%), Sjogren’s (80%), scleroderma (30-90%), PM/DM (40%), PAPS (40%), AA (30%), JRA (30%)
  - Nonrheumatic disease: Autoimmune hepatitis (100%), autoimmune thyroid disease (30-50%), chronic ILD (20%), lymphoma, neoplasms, infections (varies)
  - Normal individuals: Varies from 1-3% in healthy young adults to 10-15% in pts over 65. Low titer (< 1:160).
    - First degree relatives of pts with SLE (25%)

### ANA predictive value

- Asymptomatic individuals
  - Only 6% with low titer ANA will develop SLE over next 24 months
- Patients with one manifestation of SLE (ITP, discoid lupus, false +RPR)
  - A positive ANA increases risk for evolving into SLE from 10% to 80%
- Present ordering habits
  - PPV of positive ANA is 10% for SLE and 30% for any rheumatic disease
  - NPV of a negative ANA for SLE is 100%

### Evaluation of a positive ANA

- Hx and P/E: rule out occult Sjogren’s
- Consider repeat ANA in another lab
- ANA profile:(see addendum)
  - Anti-SS-A: SLE, Sjogren’s, UCTD
  - Anti-SS-B: Sjogren’s
  - Anti-U1 snRNP: MCTD, SLE, scleroderma
  - Anti-Sm (Smith): SLE
  - Anti-dsDNA: SLE
  - Anti-centromere: CREST
  - Anti-topoisomerase I/SCL-70: diffuse scleroderma
  - Anti-PM-SCL/PM-1: polymyositis/scleroderma overlap
  - Anti-histone: drug-induced lupus, SLE, others

PEARL: A positive ANA against a specific antigen is never normal
Evaluation of a positive ANA

- CBC (anemia: ACD vs hemolysis; leukopenia; thrombocytopenia), chemistries (kidney), LAEs, CPK, urinalysis
- ESR, RF, C3/C4 (hypocomplementemia)
- SPEP (polyclonal gammopathy), PTT (lupus anticoagulant), RPR (false positive)
- Others (patient specific): antithyroid antibodies, antihistone antibodies (DILE), anticardiolipin antibodies (hx of clot), anti-ribosomal P antibodies (psychosis or severe depression)

Case

- ANA profile: no specific antibodies
- CBC (high plts), chemistries/U/A show kidney involvement, LAEs abnormal
- CPK, PTT normal
- C3 69 (nl 82-140), C4 8 (nl 16-45)

Complement

- High complement levels indicate active inflammation and are part of the acute phase response
- Hypocomplementemia
  - CVD: SLE, cryoglobulinemia
  - Vasculitis: PAN (25%), urticarial vasculitis
  - Infection: SBE, hepatitis B viremia, parasitemia
  - Glomerulonephritis: Post-streptococcal, membranoproliferative
- Complement deficiency
  - Screen with CH50 which will be zero if a patient has a complement deficiency. Most common complement deficiency associated with an SLE-like syndrome is C2 deficiency
Case summary

- 52yo woman with arthritis, myalgias, LCV, peripheral neuropathy, and glomerulonephritis
- Abnormal routine labs support ACD, elevated pltS and low albumin as acute phase response, elevated creatinine and abnormal urinalysis reflecting kidney disease, and elevated LAEs

Case summary

- ESR and CRP are elevated consistent with acute phase response and tissue injury from vasculitis
- SPEP shows polyclonal gammopathy consistent with chronic immune stimulation
- Positive RF and ANA are nonspecific but associated with low complement levels support an immune complex mediated disease.

Differential diagnosis

- SBE: poor dentition, murmur, systemic sxS, abnormal labs (ESR, CRP, RF, low C3/C4). Lack of fever against the diagnosis of SBE.
- SLE: female, multiorgan involvement, abnormal labs (ESR, CRP, RF, ANA, low C3/ C4). No specific autoantibodies
- Sjogren’s: female, dry mouth, systemic sxS, abnormal labs (ESR, CRP, RF, ANA). No specific autoantibodies, low complements, GN doesn’t support diagnosis of Sjogren’s.
Differential diagnosis

- Lymphoma: systemic sx, abnormal labs (ESR, RF, ANA, spike). No adenopathy, low complements, GN, nl CXR doesn’t support lymphoma diagnosis
- Wegener’s: hx sinus disease, systemic sx, GN, abnormal labs (ESR, CRP, RF, ANCA). Low complements, nonspecific ANCA, nl CXR doesn’t support Wegener’s diagnosis.

Antineutrophil cytoplasmic antibodies (ANCA)

Caveats on ANCA

- ANCAs are antibodies that react with cytoplasmic antigens in ethanol-fixed neutrophils. They are screened for by an indirect immunofluorescence assay.
- ANCA should be ordered in patients with pulmonary-renal syndromes or RPGN
- ANCA associated with five diseases: Wegener’s, microscopic polyangiitis (MPA), Churg-Strauss syndrome, cocaine vasculitis, idiopathic rapidly progressive pauciimmune GN.
ANCA predictive value

- cANCA
  - Directed against serine proteinase -3 (PR-3) 90% of time
- pANCA
  - Directed against myeloperoxidase (MPO).
  - If antiMPO negative then much less likely to be associated with a
    vasculitis.
- Disease associations:
  - Wegeners (+ANCA 90%): cANCA 70%, pANCA 20%
  - Microscopic polyarteritis (+ANCA 80%): cANCA 30%, pANCA
    50%
  - Churg-Strauss (+ ANCA 60%): cANCA 15%, pANCA 45%
  - Cocaine-associated vasculitis (levamisole)(+ANCA and/or pANCA
    with or without anti-MPO positivity. Most anti-human neutrophil
    elastase (HNE) positive.
  - RPGN (+ANCA 80%): cANCA 40%, pANCA 40%

Case

- 53yo female with
  - Dry mouth, polyarthralgias/arthritis, myalgias, LCV, peripheral neuropathy, GN, HBP
  - Hx of surgery and transfusion in past
  - ACD, Creatinine, LAEs, U/A,
  - ESR, CRP, RF, low complements, polyclonal gammopathy with small spike
  - Low titer ANA and nonspecific pANCA

A diagnostic test was performed

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Cryoglobulins/Hepatitis C

Cryoglobulins

- Cryoglobulins are immunoglobulins that undergo reversible precipitation in the cold (4°C).
- Clinical features of cryoglobulinemia
  - Purpura
  - Arthralgias
  - Nephritis
  - Neuropathy
  - Acrocyanosis with digital ischemia
  - Labs: ESR, CRP, RF (if IgM), low complements

Cryoglobulinemia

- Types
  - Type I: monoclonal (usually IgM)
    - Associated with heme malignancies
  - Type II: monoclonal Ig complexed to a polyclonal IgG
    - If IgM then will have positive RF
  - HepC (50%), Sjogren’s, heme malignancies
  - Type III: polyclonal Ig (usually IgM) complexed to polyclonal IgG
    - If IgM then will have positive RF
  - CVD, hepC, chronic infections
- Hepatitis C: 50% have cryos but only 5% develop cryoglobulinemic vasculitis. Cryoglobulins contain hepatitis C RNA and anti-hep C antibodies
CASE

- Cryoglobulins 2%. Analysis showed it was type II IgM/IgG mixed cryo
- Hepatitis C positive by RIBA and PCR

FINAL DIAGNOSIS:
Hepatitis C-associated type II mixed cryoglobulinemia

Thank you
Questions ???

Bibliography
Bibliography
