



RhAPP

RHEUMATOLOGY ADVANCED
PRACTICE PROVIDERS

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The POSITIVE ANA MYTH

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Objectives

- In this presentation, we intend to show that a positive ANA does not always lead to a rheumatologic disease or diagnosis.
- ANA screening should not be first line laboratory testing as initial workup outside of Rheumatology.

Background

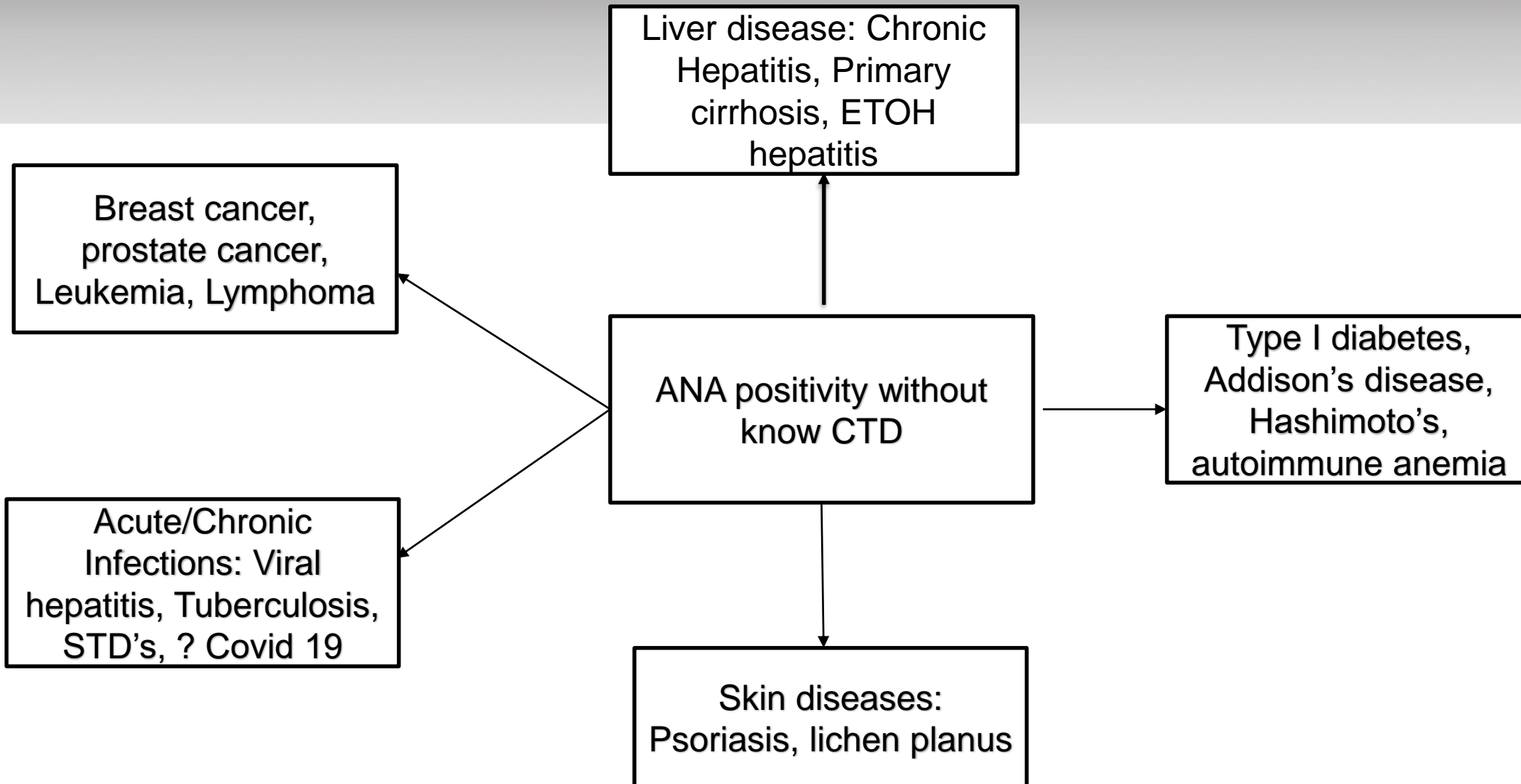
- Antinuclear antibodies can be found in approximately 40 % of healthy individuals.
- A large majority of patients with an ANA will not be due to an underlying Rheumatologic condition.
- In fact, Active Autoimmune diseases are found in only about 5 to 7 % of these individuals.
- We are here today to discuss many reasons we may see a positive ANA outside the setting of Rheumatologic disease.

Epidemiology

- What is an ANA?
- The immune system makes proteins called antibodies. These antibodies are what will attack infectious organisms. Antibodies gather proteins and cells to attack the infectious organism by causing inflammation. Antinuclear antibodies are autoantibodies that accidentally attack natural proteins within the nucleus of a cell in our bodies. This is very common. Most of the population have a small amount of these autoantibodies.
- ANA test has a very high sensitivity and a low specificity. The best way to test ANA is by using indirect immunofluorescence microscopy performed on Hep-2 cells (IIFA on Hep-2). This test looks for the presence of the antibody, as well as titer and pattern.

False Positive AnA

- Normal IIFA method will measure 1:20 ANA in healthy individuals, but that can go up to 1:160 in 1% of the tests. This type of titer fluctuation can be due to non-specific adsorption of antibodies and the presence of other antigens that are similar components the test is measuring.
- False positives are commonly due to cross reactions.
- Many antigen antibody reactions that occur with the IIFA method may not be related to autoimmune disease.
- Approximately 150 different nuclear antigens, and only a small percentage of this is associated with Rheumatologic disease.



Positive Ana and estrogen

- Positive ANA occurs more often in women.
- Autoantibodies are higher in women during their reproductive years, peaking at age 40-49 years.
- Immune response occurs when Estrogen reacts with T-helper 2 lymphocytes interacting through receptors found in many cells in the immune system.
- Estrogen receptors are found in T and B lymphocytes.
- Females produce a greater response to infection/immunization due to higher immunoglobulin levels.

Case Study-Estrogen

- 54 y/o post-menopausal female with PMH of OA presenting with rash, joint pain and ANA 1:40.
- Meds: Premarin, Estradiol, Prometrium, Singulair, Allegra, Maxalt, HCTZ
- Subj: c/o hand, hip, shoulder, and back pain. Non-pruritic Erythematous macular rash to chest. Using Tylenol PRN. Denies malar rash, oral ulcers, Raynaud's, fever, alopecia.
- Obj. No synovitis, Heberden's nodes present. Full ROM. Rash noted to chest as above. X-rays of the bilateral hands reveal degenerative changes, no erosions. Repeat Serologies revealed a positive ANA 1:160 DFS with CTD profile, and dsDNA negative. Sed rate, CRP normal. RF, CCP and HLA-B27 were negative.

Case study Cont.

- A/P-referred to Dermatology for evaluation of rash. Discussed decreasing doses of hormone supplementation with GYN. Try Turmeric for joint pain. F/u as needed.

Ana and anti-dsf70 (dense fine speckled pattern)

- Dense fine speckled pattern-most prevalent pattern found in positive ANA.
- DFS pattern is more prevalent in women.
- Rarely associated with the development of CTD.
- Most common cause of DFS pattern-allergic disease.
- Patients with Cancer most commonly will have a DFS pattern with ANA positivity.

Vitamin D and positive ana

- Vitamin D deficiencies are common in individuals with SLE.
- Vit. D deficiencies have been associated with False positive ANA in healthy individuals.
- Vitamin D stimulates the production of B lymphocytes and immunoglobulins. Leading to antibody production.
- Vit. D deficiency may contribute to the development of autoimmune antibodies.
- Patients with a severe Vit. D deficiency have a 3% increase in ANA positivity.
- Correction of Vit. D deficiency can change a positive ANA to negative ANA.

CASE Study -Vitamin D deficiency

- V.J.-55 y/o Morbidly obese female, nonsmoker with PMH iron deficiency anemia, IBS, GERD referred for low back pain, lower extremity pain, muscle cramping, and a positive ANA 1:80
- Meds: Montelukast 10mg, PRN Naproxen
- Subj.-LE pain in the hips and knees, intermittent electrical shock sensations in her LE's as well as muscle cramping. Denies rashes, oral ulcers, hair loss, discoloration to the fingers/toes, joint swelling
- Obj.- Ht. 65in, Wt. 301, BP 130/80. She has no swelling, or tenderness in the peripheral joints, knees are painful upon standing. Mild decreased vibratory sensation in both feet.

Case study cont.

- Serologies reveal a positive ANA 1:320, Sm, RNP, SS-a/b, Scl 70 neg., dsDNA neg. C3/C4 WNL, CCP, RF, and HLA-B27 neg. sed rate 12, CRP 20, Hgb 10.2, Hct 30.3, WBC, PLT wnl, CMP wnl. Vit. D-4.8
- X-rays- L-spine mod.-sev. degenerative changes, SI joints-mild DJD, bilateral knees with moderate deg. Changes
- A/P-prescribed Ergocalciferol 50,000IU, encouraged exercise, weight reduction. Returned to clinic in 3 months, Vit. D 22, continued supplement. 9 months later ANA negative Vit. D 26 (now on OTC supplement) sent for NCS which she has not completed.

ANA positivity in Liver disease and infection

- Autoantibodies which can cause a positive ANA can be found in patients with Viral Hepatitis, Drug induced Hepatitis, Alcoholic Liver disease, NASH, and Hepatocellular carcinoma.
- Treatment with Interferon for Hep. C may lead to the development of auto-antibodies.
- Autoimmune liver diseases: Autoimmune Hepatitis, Primary Biliary Cirrhosis, and Primary sclerosing cholangitis will likely result in ANA positivity.
- There is molecular mimicry in E-Coli in a target antigen, human PDC-E2. Resulting in increased mitochondrial antibodies, which can trigger positive ANA.

Infection Cont.

- One study compared the relationship of positive ANA and infection revealing that 43 patients out of 110 positive ANA patients were found only to have infections and no rheumatological diseases.
- Common pathogens associated with positive ANA are *Mycobacterium tuberculosis*, *Treponema pallidum* (syphilis), *Orientia tsutsugamushi* (scrub typhus), *E. Coli*, *Bartonella Henselae* (cat scratch disease), and *HIV*.
- Recent studies have looked at the association of ANA positivity in SARS-Co-2. Only few studies to date, one study out of Italy comparing 40 healthy controls to 40 infected. 57% of infected tested positive for ANA while 12.5% healthy controls tested positive.

Case Study: Infection

- W.M. 66 y/o male with a hx of extensive DJD of the Lumbar spine and cervical stenosis referred for positive ANA and positive RF. Seeking Rheumatologic clearance for spinal surgery. Prior workup in 2017 revealed prior RF positivity, but no evidence for RA
- Subj: He reports daily low back and neck pain, as well as hand pain. Back stiffness last all day. Hands loosen up within an hour. Taking Gabapentin 300 mg QD, and Benicar 40 mg QD. Meloxicam beneficial in the past, he is unsure why it was stopped. Not much benefit with Tylenol. He denies joint swelling, rashes, oral ulcers, Raynaud's, hair loss. Manual laborer, Smoker, daily ETOH consumption.
- Obj. Exam limited ROM to C-spine, pain with ROM of L-spine. No weakness. Heberden's and Bouchard's nodes, no active synovitis.

Case study Cont.

- Serologies: U/A, CBC, CMP-WNL's, ANA 1:80(spindle pattern) with negative profile, normal complements and negative dsDNA. RF 34, CCP abs negative, Sed rate 5, CRP <1, HLA-B27 negative. Hepatitis panel Hep CV ab >11.0, Hep. CV RNA quant. 5,000,000
- X-rays of the bilateral hands reveal moderate to severe joint space narrowing of the DIP joints without erosions. Bilateral feet and ankles were unremarkable.
- Prescribed Meloxicam 15 mg daily
- Referred to Hepatology for suspected Hep. C infection.

Positive Ana and Cancer

- Autoantibodies are found in neoplastic diseases
- Frequently found in Lung, Breast, Head and Neck cancer as often as with Rheumatoid Arthritis and Systemic Lupus Erythematosus.
- Studies have shown that as many as 9% of patients referred to Rheumatology for ANA positivity, are found to have a neoplasm instead of Rheumatologic disease.
- Most common pattern associated with neoplastic disease is DFS pattern.

Case study Cancer

- 55 y/o female with PMH of Obesity, Breast CA s/p chemotherapy and currently taking Anastrozole presenting with joint pain, LE neuropathy. Referred by Heme/Onc for evaluation of a positive ANA.
- Subjective: Severe neuropathic pain to LE's. Generalized joint pain, manageable with Cymbalta 60 mg. Symptoms started at onset of chemotherapy. No rashes, joint swelling, discoloration to the fingers, oral ulcers, fevers.
- Exam abnormal vibratory sensation to bilateral LE's, Heberden's and Bouchard's nodes, but no active synovitis.
- Serologic workup revealing mildly elevated sed rate and CRP, ANA 1:160 DFS pattern with negative profile, normal complements and negative dsDNA. Prior X-ray of L-spine with DJD

Case study Cont.

- NCS was ordered and revealed bilateral polyneuropathy of LE's.
- Initially started on Gabapentin 300 mg at HS and after 2 months was increased to 300 mg TID with reported benefit.

ANA and Autoimmune Thyroid disease

- Autoimmune thyroid disease (ATD) is the most common organ specific autoimmune disease.
- Approximately 11% of the general population is affected by ATD.
- 45% of patients with positive thyroid antibodies will concurrently have a positive ANA.
- Studies show that patients with ATD have a higher prevalence of testing positive for ANA and Rheumatoid Factor, without having clinical signs of rheumatic disease.
- Studies have shown that dense fine speckled (DFS) ANA pattern is most closely associated with patients having ATD.

Case Study: Hashimoto's

- J.W. CC Neck pain and fatigue. Reported hx of Graves disease (radioactive iodine tx) "Lupus" (prior HCQ, prednisone and Percocet), and Fibromyalgia Syndrome previously treated with Gabapentin and Cymbalta (no benefit). Taking PRN Alprazolam 1mg. Surgical hx of breast augmentation. Subj.- She reports daily low back and neck pain. Works clerical in an office setting. Fatigue interfering with her ability to perform her job. She does not exercise. She denies malar rash, Raynaud's, oral/nasal sores, or joint swelling. She mentions dry skin and mild hair loss.
- Exam: no tender or swollen joints, skin intact without rash. Paracervical TTP with spasm. No weakness, normal forward and lateral bending. 6/18 trigger points.

Case Study Cont.

- Serologies: ANA 1:320 DFS pattern. ScL-70, Sm, RNP, SS-a/b neg. Complements WNL and dsDNA were negative. HLA-B27, RF, CCP abs neg., Sed rate, CRP unremarkable. CBC, CMP WNL's, TPO ab 339 (0-34), TG, 1.0, TSH 5.850 (.450-4.500), Vit. D 11.4
- X-rays- C-spine-straightening of cervical lordotic curvature with mild disc space narrowing C5-C6. L-spine mild levoscoliosis
- Discussed PT for low back and neck-patient declined. Encouraged low impact exercises and suggested retrying Cymbalta-she will discuss with her psychiatrist. F/U with PCP regarding abnormal TSH. Ergocalciferol prescribed for Vit. D deficiency

Covid -19 and autoantibodies

- Studies are emerging since the start of Covid-19 pandemic with new information on infection and autoantibodies.
- In the beginning of the pandemic, it was proven that severe cases of Covid-19 produced autoantibodies due to the stress on their immune system.
- Study out of Cedars-Sinai found that patients with prior SarsCov2 infection had autoantibodies present 6 months following full recovery.
- This study further showed that mild to asymptomatic cases had the presence of elevated autoantibodies as well as persistence of these antibodies over time.

Covid-19 Autoantibodies CONT.

- Autoantibody activity is often linked to chronic inflammation and injury involving specific organ systems and tissue.
- Current ongoing study (Cedars-Sinai) looking at the relationship between present autoantibodies and patients with persistent Covid-19 long haul symptoms.
- Another recent study revealed that patients with autoantibodies prior to Covid-19 infection accounted for 20% or more of severe or fatal Covid-19. ? If SARS-CoV2 may result in the production of autoantibodies in those that didn't have them present prior to infection.
- The study compared 150 hospitalized with Covid-19 (over half of the subjects had presence of 1 autoantibody) to 41 healthy subjects (15% had autoantibodies).

Cont.

- In this same study, 50 of those infected with Covid-19 had blood drawn at admission and throughout the course of their hospitalization. What was found is that 20% of patients did not have autoantibodies at admission, but went on to develop autoantibodies during their hospitalization.

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