When to Suspect Autoimmune Disease

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Disclosures

* No relevant financial relationships
Objective

* To examine cases where an autoimmune diagnosis might be considered.

* To evaluate the value of diagnostic testing and when a rheumatology referral may be beneficial
Case 1: ANA in the Worried Well
  - Objective Signs of Inflammation
  - The ANA test
  - ESR and CRP

Case 2: Sjogren’s Syndrome
  - Classification Criteria in Rheumatic Diseases

Case 3: Raynaud’s phenomenon
  - Nailfold Capillaroscopy

Case 4: Fibromyalgia
  - 3 types of Joint Pain

Last Thoughts
Ms. Disquiet is a 52yo obese woman with diabetes who asked her primary care doctor to order an ANA, because she read on the internet that her fatigue could be a sign of lupus. She has a sedentary lifestyle because of generalized joint pain with activity.

Her ESR was 26 (normal 0-20) and CRP was 8 (normal 0-7 mg/L).
1. Order the ANA because you are running behind and it is an easy test to order.

2. Not order the ANA and spend the next 15 minutes explaining why it is unnecessary.
Objective Signs of Autoimmunity

- Red, hot, swollen joints
- Rash
- Abnormal blood tests
- Pathological weakness
True arthritis not arthralgias
Lupus Rashes

Photosensitivity

Nasolabial sparing

Rashes between finger joints
Lupus Malar Rash vs Rosacea

Nasolabial sparing

No nasolabial sparing
Livedo reticularis

- Appears in a broad-based **interrupted** pattern in systemic vasculitis, including lupus
- May occur as a fine, connected, lacy pattern in normals
Palpable Purpura

- Seen in cutaneous vasculitis
- Example: Henoch-Schönlein purpura
Saddle nose deformity

- Relapsing polychondritis
- May also occur in syphilis and ANCA associated vasculitis (AAV, aka Granulomatosis with Polyangiitis (GPA), previously known as Wegener’s granulomatosis)
Hypermobility

- Ehlers-Danlos Syndrome is a true connective-tissue disease
- Left: True hypermobility of joints. Can touch thumb to volar surface of forearm
- Right: Hyperelasticity of skin
- Associated with vascular abnormalities
ANA
poor specificity (lots of false positives)

- At 1:40 dilution, 31.7% of normals +
- At 1:80 dilution, 13.3% of normals +
- At 1:160 dilution, 5% of normals +
- At 1:320, 3% of normals +

The ANA: a nonspecific test
Positive ANAs in people without autoimmune disease

* 15-25% of fibromyalgia patients*

* 5-25% of healthy relatives of lupus patients*

The ANA: a sensitive test

*good sensitivity  (few false negatives)*
- At 1:40 dilution, 99% of SLE patients +
- At 1:80 dilution, 97.4% of SLE patients +

Very Sensitive for SLE, but very Nonspecific

So a negative ANA rules out lupus.
Tests looking for organ specific autoimmune disease

- UA, BUN, Creatinine - SLE criteria
- CBC - SLE criteria
- TSH - autoimmune thyroiditis
- LFTs - autoimmune hepatitis
- CPK - polymyositis
Disease prevalence matters
What test could be positive even if the ANA were negative?

* 1. SSA
* 2. dsDNA
* 3. anti-RNP
* 4. SSB
* 5. anti-Scl-70
What test could be positive even if the ANA were negative?

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Which test would be most worrisome for autoimmunity?

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What these tests may indicate

* 1. SSA-Sjogren’s syndrome (SS)
* 2. dsDNA-thought be specific for lupus
* 3. anti-RNP-Mixed Connective Tissue Disease (MCTD)
* 4. SSB-Sjogren’s syndrome (SS)
* 5. anti-Scl-70-systemic sclerosis (scleroderma)
Case 1: Ms. Disquiet

- Ms. Disquiet is a 52yo obese woman with diabetes who asked her primary care doctor to order an ANA, because she read on the internet that her fatigue could be a sign of lupus. She has a sedentary lifestyle because of generalized joint pain with activity.
- Her ESR was 26 (normal 0-20) and CRP was 8 (normal 0-7 mg/L).
Her ESR was 26
Age adjusted ESR upper limit of normal (ULN) = age/2
If woman +10
So her ESR ULN = 52/2 + 10 = 36. So her ESR was not actually elevated
And her CRP?

- CRP was 8 (normal 0-7 mg/L)
- Age adjusted CRP ULN=age/5 (mg/L) or age/50 (mg/dl) *
- If woman +6 (mg/L) or +0.6 (mg/dl)
- So 52/5+6=16.4 mg/L CRP ULN.

Mrs. Arid is a 60 yo woman who presents with dry eyes, dry mouth, and progressive facial swelling for the past 2 months.
Case 2: Mrs. Arid
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What is the most important test to get in this patient?

1. ANA
2. SSA/SSB
3. Parotid gland biopsy
4. CBC c/diff
5. SPEP/UPEP
6. PA/lat CXR
What is the most important test to get in this patient?

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4-8% of Primary Sjogren’s patients will have B cell lymphoma.*

1. Objective measure of eye and mouth dryness

2. An indication of autoimmunity
Sjogren’s Syndrome (SS) Diagnosis

* Criteria 1:
  * The patient has an objective marker of dry eyes or dry mouth
    * Schirmer test in either eye of <5 mm/5 min or abnormal ocular surface staining
    * Salivary hypofunction (abnormal Saxon test or whole sialometry)
    * Magnetic resonance imaging (MRI) or ultrasound (US) evidence of significant glandular parenchymal abnormalities characteristic of SS.

* Criteria 2:
  * Positive anti-Ro/SSA and/or anti-La/SSB antibodies
  * Positive lip biopsy (ie, focal lymphocytic sialadenitis with focus score ≥1) or a well-established systemic rheumatic disease (eg, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, or idiopathic inflammatory myopathy).
  * Anticentromere antibodies (in the absence of systemic sclerosis) or the combination of an antinuclear antibody (ANA) ≥1:320 with a positive rheumatoid factor. “Secondary SS” is considered in patients with lacrimal and salivary gland dysfunction and a well-established systemic rheumatic disease.

* Often confirm weakly positive tests for anti-Ro/SSA or anti-La/SSB with a lip biopsy.

Classification Criteria are used to make homogenous study populations to study a particular disease, and were not designed for daily clinical practice.

2002 American-European Consensus Group (AECG) criteria
Need 4 of 6. Gold standard was clinical observations of expert clinicians.

- Symptoms of ocular dryness
- Ocular signs of inadequate tear production
- Symptoms of oral dryness
- Tests indicating impaired salivary gland function or altered structure
- Salivary gland histopathology demonstrating foci of lymphocytes
- Presence of autoantibodies (anti-Ro/SSA and/or anti-La/SSB)
2002 American-European Consensus Group (AECG) criteria

Exclusion criteria – Patients who would otherwise fulfill the classification criteria are excluded if any of the following disorders is present:

• Prior head and/or neck irradiation
• Infection with hepatitis C virus (HCV)
• Acquired immunodeficiency syndrome (AIDS)
• Lymphoma
• Sarcoidosis
• Graft-versus-host disease
• Recent use of medications with anticholinergic properties
Primary SS

Primary SS –no associated connective tissue disease and no exclusionary diagnoses cited above, a classification of primary SS can be made according to the consensus rules in one of two ways:

• The patient has either a positive salivary gland biopsy or anti-Ro/SSA and/or anti-La/SSB autoantibodies and satisfies a total of four of the six items. This rule is associated with a sensitivity of 97 percent and a specificity of 90 percent.

• The patient satisfies three of the four objective items (ocular signs, biopsy, salivary gland involvement, or autoantibodies). This rule has a sensitivity of 84 percent and a specificity of 95 percent.

Secondary SS –**connective tissue disease is present** and if both of the following criteria are met:

- Symptoms of ocular or oral dryness

- Any two of the following three objective items are present:
  - Ocular signs
  - Positive salivary gland biopsy
  - Abnormal tests of salivary gland function

The associated connective tissue diseases include systemic lupus erythematosus, systemic sclerosis (scleroderma), rheumatoid arthritis, mixed connective tissue disease, inflammatory muscle disease, autoimmune liver disease, and autoimmune thyroid disease.

Keratoconjunctivitis Sicca
Xerostomia
Normal Schirmer’s Test 15mm

- Abnormal would be <5mm/5 minutes
Case 3: Miss Frosty

A 32yo previously healthy woman presents with fingers that turn white and cold in the winter. This started last winter. She has no other symptoms.
Episodic, reversible digital skin color change
- white to blue to red
- well-demarcated
- due to vasospasm, cold/stress induced

* Occurs in 5-10% of men, up to 20% of women. 10-12% may develop a collagen vascular disease.

* Treatments: calcium channel blockers, topical nitrates, phosphodiesterase type 5 inhibitors
Case 3: Miss Frosty
What is the most beneficial next test?

* 1. Hgba1c
* 2. ANA
* 3. CT Chest
* 4. EGD
* 5. Nailfold Capillaroscopy
What is the most beneficial next test?

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Answer: 5. Nailfold Capillaroscopy
Raynaud’s: Primary vs Secondary (Autoimmune?)

Nailfold capillaroscopy

http://www.slideshare.net/SclerodermaUK/what-is-raynauds-what-is-scleroderma
DM and SSc: periungual involvement

uniform morphology and homogeneous distribution of small capillary loops just below the cuticle.

dcSSc: dilation of isolated capillary loops, with loss of surrounding loop structures.

adult DM: loss of normal homogeneous distribution of the capillaries and alterations in morphology of vessels, including the dilated and enlarged "giant" capillary loops.

childhood DM: Dilated capillary loops, areas of arborized clusters of capillary loops.
Only need some magnification
Enlarged capillaries were found in 100% of SSc patients, 86% of DM patients, and 56% of UCTD patients.*

Positive predictive value of the presence of megacapillaries for a scleroderma spectrum disorder (SSD) was 63.5%*

Negative predictive value of a normal capillaroscopy 96.7%*

No special equipment needed

- Can use an common ophthalmoscope, increasing magnification to 40.
- Use any clear gel for magnification.
- Study cited below noted no major differences in examination effectiveness with a modified dermatoscope compared to more expensive capillaroscopes.

Mrs. Dolores is a 55yo woman with DM, HTN, and depression who presents with diffuse pain and tenderness in both joints and muscles. She also feels weak and chronically tired.
Which is not a Choosing Wisely Initiative of the ABIM and ACR?

* 1. Do not order autoantibody panels without a positive ANA and evidence of a rheumatic disease.
* 2. Laboratory tests should be used to confirm your clinical diagnosis not make it.
* 3. Do not test for Lyme disease as a cause of musculoskeletal symptoms without an exposure history and appropriate examination findings.
* 4. Do not order an MRI of the spine within the first 6 weeks in patients with nonspecific low back pain in the absence of red flags (trauma, use of corticosteroids, unexplained weight loss, progressive neurologic signs, age > 50 years or < age 17 years, fever, IV drug abuse, pain unrelieved by bed rest, history of cancer).
1. Do not order autoantibody panels without a positive ANA and evidence of a rheumatic disease.

2. **Laboratory tests should be used to confirm your clinical diagnosis not make it.**

3. Do not test for Lyme disease as a cause of musculoskeletal symptoms without an exposure history and appropriate examination findings.

4. Do not order an MRI of the spine within the first 6 weeks in patients with nonspecific low back pain in the absence of red flags (trauma, use of corticosteroids, unexplained weight loss, progressive neurologic signs, age > 50 years or < age 17 years, fever, IV drug abuse, pain unrelieved by bed rest, history of cancer).

* Answer: 2. Although true, 2 is not a Choosing Wisely Initiative.
3 types of joint pain

* 1. Structural
* 2. Inflammatory
* 3. Fibromyalgia

* From Gardner’s Rules of Rheumatology, Rule 2
INFLAMMATORY

- Redness, swelling, warmth, **morning stiffness >1 hour**, pain better with activity, **erosions** on x-rays
- Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, reactive arthritis

NON-INFLAMMATORY (MECHANICAL)

- Loss of cartilage, reactive bone formation leading to osteophytes and bone spurs Morning stiffness <1 hour
- Gelling can occur (**stiffening with inactivity**), pain worse with activity, joint space narrowing on x-rays
- Osteoarthritis
Case 4: Mrs. Dolores
Fibromyalgia (FM)

- Joint pain without objective inflammation is not a criteria worrisome for autoimmunity.
- Pseudo-neurologic symptoms are common in FM
- True myopathies typically have more weakness then pain.
- Myopathies tend to cause proximal symmetric weakness.
- Neuropathies tend to cause distal and asymmetric weakness with muscle atrophy
Outline

* Case 1: ANA in the Worried Well
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* Last Thoughts
When thinking of rheumatic disease, typically need to **rule out infection and malignancy** first.

Common things are common, so the 64 yo man with a fever, SOB, and a lung infiltrate will have pneumonia the vast majority of the time.

Rheumatic diseases are very uncommon, therefore one’s threshold for diagnosing one should be fairly high.

A careful history and physical exam is far and away the most important component in diagnosing rheumatic disease.
What’s In?

- Focal joint inflammation (swelling, redness, warmth, and tenderness)
- Rashes (palpable purpura, photosensitive dermatitis)
- Uveitis

What’s Out?

- Fatigue
- Diffuse joint and muscle pain
- Dry eye and mouth sensation with exuberant tear and saliva production
Credits

* Dr. Ina Oppliger
* Dr. Gregory Gardner
* Other UW Fellow Talks
* UptoDate
* Rheumatology Secrets 3rd Ed. by Sterling West
* Rheumatology 6th Ed. by Marc Hochberg et al.
* http://rheumaknowledgy.com
* Individual Studies are cited with each slide
Questions?