Categories of Rheumatic Diseases with their Immune and Laboratory Correlates

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Conflict of Interest Disclosure

I have no conflicts and nothing to disclose

Learning Objectives

1) To grasp the General CATEGORIES of Connective Tissue Diseases
2) To understand the Step Approach to their diagnosis (History, Exam, Lab, Imaging, Taps, Bx…)
3) Utilize CLASSIFICATION CRITERIA for definitive diagnosis
Lecture Outline

Categories of Degenerative & Immune Disease

I) Regional Musculoskeletal Abnormalities
   - Osteoarthritis & degenerative spinal disease

II) Inflammatory Diseases (Sero-Negative)
   - SpondyloArthritis Group
   - Polymyalgia Rheumatica

III) AutoImmune Diseases: (Sero-Positive)
   - Systemic Lupus
   - Rheumatoid Arthritis

IV) Vasculitic Syndromes
   - Large, Medium & Small vessel Dz

General Principals in the Diagnosis of Inflammatory & Autoimmune Diseases

1) Carefully perform History & Physical
   (Is there a Suspicion of an Immune Disease?)
2) Order screening lab tests: CRP, ANA, RF, CCP, etc…
   Aspirate, biopsy and analyze your data
3) Next order specific auto-antibody titters: Sm, DNA…
4) Utilize the Categories & Diagnostic Criteria
5) Evaluate Dz activity; DZ activity scores & labs
   CRP, ESR, C4, C3, gamma globulin levels
6) Evaluate major organ systems

Statements on Rheumatic Labs

- Requires an elevated suspicion of Immune Dz
- Your Initial Clinical Impression is your guide to the diagnosis
- Sensitive, but sometimes non-specific
- Immune labs serve as confirmatory data
- Many patients with a pos RF & ANA do not have RA & SLE
- In acute presentations rule out infections as an etiology for positive rheum labs

Genetic & Epigenetic Abnormalities

Environmental exposures:
1) Ultraviolet rad
2) Smoking
3) Periodontal dz
4) Infections
5) Mammals
6) Virus

Loss of Immune Tolerance

Dysregulation activates Autoimmunity

Immunodeficiency

Autoimmune disease:
SLE, RA, SJOG, SS, Myositis, etc.

Malignancies

Categories of Connective Tissue Diseases

0) Regional Musculoskeletal Abnormalities
- Osteoarthritis and associated degenerative disorders

II) Inflammatory Diseases (Sero-Negative)
- Arthritis 2" to legitimate immune response:
  • Infections: Active Vs Reactive, Gynaecopathies, Metabolic disease....
  • Primary inflammatory conditions: Spondyloarthritis, PMR ...
  • Auto-Inflammatory Diseases: Hereditary Periodic Fever
  • Malignancies: MGUS, Plasmacytoma, MM, Lymphomas...

III) Auto-Immune Diseases: RA, SLE, SS, Sjog etc.

IV) Vasculitic Syndromes

Regional Musculoskeletal Diseases

Characterized:
- History:
  • Pain exacerbated by activity and relieved by rest
  • Localized Pain within weight bearing joints

- Physical Examination:
  • Localized joint hypertrophy with crepitus, tendonitis and bursitis

- Laboratory Studies:
  • All normal: ESR, CRP, ANA, RF, CCP, ANCA

- X-Rays:
  • Asymmetrical narrowing, sclerosis and hypertrophy
Degenerative Joint Disease

Osteoarthritis: First Carpometacarpal Joint

Lumbar Degenerative Disc Disease (Spondylosis)
Cervical Spine Degenerative Disc Disease

Lumbar Ankylosing Spondylitis: Syndesmophytes

Cervical Ankylosing Spondylitis: Syndesmophytes
Bone Abnormalities

**Degenerative Joint Diseases**
- Asymmetrical cartilage deterioration
- Subchondral sclerosis
- Eburnation, osteophytes
- Osseous hypertrophy
- Weight bearing joints

**Inflammatory Diseases**
- Symmetrical narrowing of joint spaces
- Periarticular osteopenia
- Syndesmophytes (bone formation)
- Osteoporosis
- Enthesitis

Categories of Connective Tissue Diseases

1) Regional Musculoskeletal Abnormalities
   - Osteoarthritis and associated disorders

2) Inflammatory Diseases (Sero-Negative)
   - Arthritis due to legitimate immune response:
     - Infections, reactive arthritis, Crystalline Dz
   - Primary inflammatory Dzs: Spondyloarthritis, PMR...
   - Auto-Inflammatory Diseases: Hereditary Periodic Fever Syndromes
   - Malignancies: MGUS, Plasmacytoma, MM, Lymphomas...

3) Auto-Immune Diseases (Sero-Positive)
   - RA, SLE, Sjogren's Synd, Scleroderma, Myositis etc...

4) Vasculitic Syndromes

Innate Immune Features

(Immunological Diseases)

- First Line of Defense
- Early Rapid Inflammatory Response
- Selective Receptors: Structures common to Microbes
- Cells: Neutrophils, Macrophages, DCs & NK cells
- Soluble portion:
  - Inflammatory mediators (cytokines): CRP, TNF, IFNs...
  - Complement System C3, C4, CH50...
- No Immunological Memory, No Autoimmunity
Features Inflammatory Diseases
(Sero-Negative)

- **History:**
  - Nocturnal and early morning Stiffness/Swelling
  - Stiffness is relieved with activity and exacerbated with rest (Gelling)
- **Physical Examination:**
  - Inflammatory joint features; synovitis, erythema, swelling, effusions and enthesitis
- **Labs:** Elevated inflammatory mediators; increased CRP, ESR & alpha-1 or 2 fraction on SPEP
  - ANA, CCP & RF are Negative (Sero-Negative Dz)
- **X-Rays:** Symmetrical narrowing, periarticular osteopenia and osteoporosis

*Secondary Inflammatory Diseases*

- **Infections:** Hepatitis-C, Endocarditis…
- **Post-Infectious reactive arthritis**
- **Crystalline arthropathies:** Gout, CPPD & Basic calcium phosphate disease etc…
- **Tic born infections:** Lyme, Ehrlichiosis, Babesiosis, RMSF etc…
- **Malignancies:** Multiple myeloma, plasmacytomas, lymphomas, leukemias etc.

*Primary Inflammatory Conditions*
(Sero-Negative)(Cytokine mediated)

- **SpondyloArthritis Group**
- **Polymyalgia Rheumatica**
- **Adult-Onset Stills Disease**
- **Hereditary Periodic Fever Syndromes** (systemic auto-inflammatory disorders)

*Spondylarthropathy Group*
(Axial & Peripheral distribution)
(Pre & Post-radiographic)

- Ankylosing Spondylitis
- Psoriatic Spondylarthropathy
- Inflammatory Bowel Disease associated Arthritis
- Reactive Arthritis (post-infectious)
- Undifferentiated Spondylarthropathy

Ritchlin C, et al. NEJM 2017; 376: 957-70

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**General Features of Spondyloarthritis (SpA)**

- Inflammatory back pain & SI joint symptoms
- Prolonged nocturnal & AM stiffness
- Peripheral Inflammatory arthritis
- Stiffness improved with exercise
- Reduced spinal & chest mobility over time
- Enthesitis & syndesmophytes (bone formation)
- Extra-skeletal manifestations
- Elevated ESR/CRP & associated HLA-B27


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**Axial Spondyloarthritis**

**Early Dz**
- Pre-Radiographic Stage
- Inflammatory back pain
- STIR MRI-sacroiliitis

**Late Dz**
- Radiographic Stage
- Inflammatory back pain
- X-Ray sacroiliitis/erosions
- Syndesmophytes

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2011 ASAS axial SpA classification criteria
ASAS classification criteria for axial spondyloarthritis (SpA) consist of:

- Clinical criteria
- Imaging criteria

CRP: C-reactive protein; NSAIDs: non-steroidal anti-inflammatory drugs.


Pathways of Bone Resorption and New Bone Formation in Patients with Ankylosing Spondylitis.


Ankylosing Spondylitis
(syndesmophytes formation “bambooing”)
Advanced Ankylosing Spondylitis
Syndesmophytes, apophyseal ankylosis & SI Fusion

Ankylosing Spondylitis
(Sacroiliitis on Ferguson view)

Sacroiliac Erosions, STIR MRI

Webber U et al. Arthritis Res Ther 2012
Psoriatic Spondylitis
(Sausage digits: pitting, swelling, erythema & onycholysis)

Psoriatic Mutilans
“telescoping fingers”
Features of Polymyalgia Rheumatica

- Age greater than 50 years
- Weight loss, fatigue & fevers
- Significant bilateral AM stiffness
- Hip & Shoulder girdle symptoms
- Elevated ESR/CRP, Negative RF, CCP, ANA
- Dramatic response to steroids
  (polymyalgia dramatica)
- PMR is associated with Giant Cell Arteritis


Immune Laboratory Testing

** Innate Immunity (Inflammatory Dz) (Spondyloarthritis, PMR etc.)
- ESR: Pos
- CRP: Pos
- ANA: Negative
- RF: Negative
- Anti-CCP: Negative
- Uric Acid: Pos/Neg
- ANCA: Negative

Adaptive Immunity (Auto-Immune Dz) (RA, SLE, Sjog, MCTD etc.)
- ESR: Pos/Neg
- CRP: Pos/Neg
- ANA: Pos → ENA
- RF: Pos
- Anti-CCP: Pos
- ANCA: Pos → PR3 → MPO

Categories of Connective Tissue Diseases

I) Regional Musculoskeletal Abnormalities
- Osteoarthritis and associated disorders

II) Inflammatory Sero-Negative Diseases
- Arthritis 2° to legitimate immune response:
  - Infections, Metabolic disease…. 
- Primary inflammatory conditions: Spondylitis, PMR ...
- Auto-Inflammatory Diseases: Hereditary Periodic Fever
- Malignancies: MGUS, Plasmacytoma, MM, Lymphomas...

III) Auto-Immune Diseases: RA, SLE, Sjogren’s synd, scleroderma, myositis, etc…
Adaptive Immunity (Antibodies)
- Delayed Onset antibody activity
- Highly specific antibodies
- Antibodies generated to a diversity of targets
- Cellular system: T-cells, B-Cells and Plasma cells
- Soluble effectors: Gamma globulins
- Immunological Memory
- Autoimmunity: SLI, RA, Sjog, Scleroderma…

Adaptive Immunity

Immunoglobulins
Rheumatoid Arthritis Defined:
- Chronic autoimmune disease with inflammatory features
- Characterized by polyarthritis with progressive joint damage, erosions, deformities, nodules and osteoporosis
- Organ involvement includes: ILD, pleuropericarditis, neuropathy, scleritis, splenomegaly, vasculitis etc.
- Multiple innate & adaptive immune abnormalities with augmented systemic inflammation
- The ideology is multifactorial

2010 Amer Coll Rheum / European League Classification of Rheumatoid Arthritis
- 1) At least 1 joint with Synovitis (swelling)*
- 2) Synovitis not explained by another disease!**
- A) Joint Involvement score (0-10 pts)
- B) Serology: RF & CCP antibody (0-5 pts)
- C) Acute phase reactants: ESR & CRP (0-1 pt)
- D) Duration of symptoms (0-1 pt)
A score of 6 needed for DX of RA

2010 Amer Coll Rheum / European League Classification of Rheumatoid Arthritis

Non-Rheumatic Conditions with a Positive Rheumatoid Factor
- Aging: (age greater than 70): 10 - 25%
- Infections: Bacterial endocarditis 25-50%, TB 8%, Syphilis 0-13%, Parasitic infections 20-90%, Viral Infections 15-65%, especially Hep-C
- Pulmonary Diseases: Sarcoidosis, Pulmonary Fibrosis 10-50%, Asbestosis…
- Primary biliary cirrhosis

Newkirk et al. J Rheumatol 2002; 29: 2034
Sansonno D, J Immunol 1998; 160: 3994
**Rheumatic Diseases Associated with a Positive Rheumatoid Factor**
- Rheumatoid arthritis (80-85%)
- Sjogren’s syndrome (75-95%)
- MCTD (50-60%)
- Primary Scleroderma (20-30%)
- Systemic Lupus (15-35%)
- Sarcoid (15%)
- Polymyositis/Dermatomyositis (5-10%)


**CCP antibody Summary**
- CCP ab is more specific for RA than RF
- Is present during the Early stages of RA
- Associated with higher disease activity, erosive disease, and worse long term outcome
- Associated with the development of extra-articular disease and organ involvement
- Assists in identifying early aggressive disease so that early aggressive treatment may be initiated


**Synovial Pathology in Rheumatoid Arthritis**
- Synovial lining hyperplasia
- Mononuclear cellular infiltrate with lymphocytes and macrophage
- Augmented angiogenesis
- Multinucleate osteoclasts form pannus destroying bone & cartilage
- Augmented cytokine production with release of collagenases, stromelysins and metalloproteinase

RA Pannus Formation
(Inflamed synovium)

Early Rheumatoid Arthritis
(Symmetrical fusiform swelling)

Chronic Rheumatoid Arthritis
Rheumatoid Arthritis

RA Atlantoaxial Subluxation

ANA: peripheral, diffuse, speckled & nucleolar
Antinuclear Antibodies

- ANA is highly sensitivity but of low specificity
- ANA (+) 30% of normal persons
- ANA (+) may pre date Autoimmune Disease*
- Other conditions with a positive ANA titer:
  - Infections, Drugs, Malignancy …
  - Organ Specific Autoimmune Dz: Thyroiditis …
  - Undifferentiated Connective Tissue Disease
  - Systemic Autoimmune Diseases
- Of all positive ANA’s only 5% will be Lupus


Development of Autoantibodies before the Clinical Onset of SLE: Dept of Defense Repository study

- 30 mil specimens were prospectively collected from 5 million US Armed Forces personnel
- The serum of 130 persons diagnosed with SLE were examined
- 115 of 130 (88%) patients with SLE had at least 1 SLE-Ab up to 9 years before diagnosis
- A predictable course of accumulating auto abs occurred
- Conclusion: Autoantibodies are typically present many years before the Dx of SLE


Kaplan-Meier Curves for the Proportion of Patients with Positive Antibody Tests Relative to the Time of Diagnosis or Appearance of the First Clinical Manifestation of SLE

Accumulation of Systemic Lupus Autoantibodies


Features of Autoimmune disease

- Morning stiffness, synovitis, tenosynovitis effusions etc.
- Raynaud's phenomena
- Photosensitivity, skin rashes, patchy alopecia …
- Ophthalmologic: episcleritis, uveitis, retinitis…
- Pleuritis, pericarditis

Harvard Medical School 2015

Classic Autoimmune Syndromes

- Undifferentiated CT Disease (UCTD)
- Rheumatoid Arthritis
- Systemic Lupus Erythematosus
- Sjogren's Syndrome
- Systemic Sclerosis / CREST Syndrome
- Mixed Connective Tissue Disease
- Inflammatory Muscle Disease
- Antiphospholipid Syndrome
- OverLap Syndromes (ex Rupus …)

Clinical Features of Systemic Lupus

- Multisystem autoimmune Dz with relapsing course
- Variable features; joint/skin dz to multiorgan involvement
- Array of Autoantibodies and Complement activation
- Ds-DNA and Smith abs have greatest specificity
- African-American, Asian & Hispanic women have the highest prevalence of disease
- Lupus nephritis is the most common life-threatening manifestation
- Accelerated atherosclerosis requires aggressive risk factor modification


Overview of the Pathogenesis of Systemic Lupus Erythematosus.


SLE Criteria (4 of 11 required)

- 1) Malar rash: fixed erythema over malar eminence
- 2) Discoid rash: raised, keratotic & atrophic scarring
- 3) Photosensitivity: Rash from sunlight reaction
- 4) Oral, nasopharyngeal & tongue ulcers: Painless
- 5) Inflammatory arthritis: Synovitis
- 6) Serositis: a) Pleuritis  b) Pericarditis

SLE Criteria (cont)

- 7) Renal disease: a) persistent proteinuria >0.5 g/d  
   b) cellular casts: Red blood cells, granular or mixed
- 9) Hematologic: a) hemolytic anemia  
   b) leukopenia; < 4000/mm  
   c) lymphopenia; < 1500/mm  
   d) thrombocytopenia; < 100,000/mm

SLE Criteria (cont)

- 10) Immunologic: 1) ds-DNA ab  2) Smith ab  
   3) phospholipid antibodies
- 11) ANA positive

Extractable Nuclear Antigens
(ANA-profile)

- anti-dsDNA Ab*: SLE & Nephritis
- anti-Smith Ab: SLE
- anti-U1-RNP Ab: SLE & MCTD
- anti-SSA & SSB: SLE, Sjogrens & fetal heart dz
- SCL-70 ab: Diffuse scleroderma
- anti-Histone Ab: SLE & Drug-SLE
- anti-Centromere Ab: Limited scleroderma
- Phospholipids: Thrombosis & Pregnancy loss
Renal Involvement-1

- Renal disease is common in SLE
- Up to 90% of SLE Pts have pathological evidence of renal Dz on biopsy
- Only 50% develop clinically significant nephritis
- Clinical presentation is highly variable from hematuria to rapidly progressive glomerulonephritis


Lupus Nephritis

Table 1: The 2003 International Society of Nephrology and International Pathology Society Classification of lupus nephritis

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Minimal mesangial lupus glomerulonephritis (MGN)</td>
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<tr>
<td>II</td>
<td>Mesangial proliferative LGN</td>
</tr>
<tr>
<td>III</td>
<td>Focal LGN (&gt; 50% glomeruli)</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse LGN (&gt; 50% glomeruli)</td>
</tr>
<tr>
<td></td>
<td>Predominantly segmental</td>
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<tr>
<td></td>
<td>Predominantly global</td>
</tr>
<tr>
<td>V</td>
<td>Membranous LGN</td>
</tr>
<tr>
<td>VI</td>
<td>Advanced sclerotic LGN (&gt; 90% sclerotic glomeruli)</td>
</tr>
</tbody>
</table>

Immune Laboratory Testing

**Innate Immunity**
- (Inflammatory Dz)
- (Spondyloarthritis, PMR etc.)
- ESR: Pos
- CRP: Pos
- ANA: Negative
- RF: Negative
- Anti-CCP: Negative
- ANCA: Negative

**Adaptive Immunity**
- (Auto-Immune Dz)
- (RA, SLE, SJog, MCTD etc.)
- ESR: Pos/Neg
- CRP: Pos/Neg
- ANA: Pos → ENA
- RF: Pos
- Anti-CCP: Pos
- ANCA: Pos → PR3
- MPO
Selected Scleroderma Spectrum Diseases

- Mixed Connective Tissue Disease
- Limited Scleroderma
- Diffuse Scleroderma

Patients with Raynaud’s Phenomenon

- Primary Raynauds (benign)
- Systemic Lupus: Sm ab, RNP ab, dsDNA ab, etc
- Sjogrens Syndrome: SSA & SSB ab

Raynauds Assoc Diseases

- MCTD: RNP (high titer ab)
- Limited Scleroderma (CREST): Centromere ab
- Diffuse Scleroderma: SCL-70, RNA Pol-III ab

Scleroderma Spectrum Diseases

- MCTD: RNP (high titer ab)
- Limited Scleroderma (CREST): Centromere ab
- Diffuse Scleroderma: SCL-70, RNA Pol-III ab

Mixed Connective Tissue Disease
- Raynauds Phenomenon
- Overlap: SLE, Scleroderma, Polymyositis
- Scleroderma, Sclerodactaly
- Esophageal dysmotility disorders
- *Interstitial Lung Disease: CXR, PFTs, HRCT
- *Pulmonary Arterial Hypertension: ECHO
- Lab Order: high titer RNP abs


Limited Scleroderma
- Slow onset of disease
- Raynauds for years, long latency period
- Skin fibrosis limited: hands, feet, face (peripheral)
- Nailfold capillary abnormalities typical for SS
- Pulmonary hypertension (10-15%)
- Renal disease rare
- Centromere abs (50-60%)


Diffuse Scleroderma
- Rapid onset of disease, aggressive damage
- Raynauds followed, within 1 year, puffy and hidebound skin
- Accelerated Nailfold capillary abnormalities
- Early and significant incidence: interstitial lung dz, diffuse GI dz, renal dz and cardiac dz
- ANA: Nucleolar, SCL-70 ab (30%) or RNA polymerase III ab.

Clinical Findings in Patients with Scleroderma in Four Countries

Lesions in Different Stages of Scleroderma

Necrosis of the Fingers and Toes
Vasculitis Types

Thank You