Autoimmune diseases

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What will we discuss today?

• Introduction to autoimmune diseases

• Some examples
Introduction to autoimmune diseases

• Chronic
• Sometimes relapsing
• Progressive damage
• Epitope spreading...more and more damage
• Actions may be by:
  - autoantibodies
  - Th1 & Th17 cells
  - CD8 cells
  - both cellular and humoral
Introduction, cont’d

• Autoimmune diseases may be

  Systemic

  Tend to involve connective tissues
  = collagen vascular diseases
  = connective tissue diseases

  Organ-specific

  blood vessels

  We will discuss some of these
Examples

• Systemic lupus erythematosus (SLE)

• Sjogren syndrome

• Systemic sclerosis
SLE

- Autoantibodies/immune complexes
- Onset: acute or insidious
- Typically: chronic, remitting and relapsing
- Often febrile illness
- 20s & 30s
- F:M ratio: 9:1...in reproductive age
- Blacks & Hispanics more

*...Skin
...joints
...kidney
...serosal membranes
...any other organ
When to suspect SLE:

ACR (Revised) Criteria for Classification
4/11= 95% Specificity; 85% Sensitivity

1. Serositis
2. Oral ulcers
3. Arthritis
4. Photosensitivity
5. Blood cells
6. Renal involvement
7. Antinuclear antibodies (ANA)
8. Immunologic disorder
9. Neurologic disorder
10. Malar rash
11. Discoid rash

## Important antibodies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Specificity of Autoantibody</th>
<th>% Positive</th>
<th>Association with Specific Disease Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Double-stranded DNA</td>
<td>40-60</td>
<td>Nephritis; specific for SLE</td>
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<tr>
<td></td>
<td>U1-RNP</td>
<td>30-40</td>
<td></td>
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<tr>
<td></td>
<td>Smith (Sm) antigen (core protein of small RNP particles)</td>
<td>20-30</td>
<td>Specific for SLE</td>
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<tr>
<td></td>
<td>Ro (SS-A)/La (SS-B) nucleoproteins</td>
<td>30-50</td>
<td>Congenital heart block; neonatal lupus</td>
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<tr>
<td></td>
<td>Phospholipid-protein complexes (anti-PL)</td>
<td>30-40</td>
<td>Antiphospholipid syndrome (in ~10% of SLE patients)</td>
</tr>
<tr>
<td></td>
<td>Multiple nuclear antigens (“generic ANAs”)</td>
<td>95-100</td>
<td>Found in other autoimmune diseases, not specific.</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>DNA topoisomerase 1</td>
<td>30-70</td>
<td>Diffuse skin disease, lung disease; specific for systemic sclerosis</td>
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<tr>
<td></td>
<td>Centromeric proteins (CENPs) A, B, C</td>
<td>20-40</td>
<td>Limited skin disease, ischemic digital loss, pulmonary hypertension</td>
</tr>
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<td></td>
<td>RNA polymerase III</td>
<td>15-20</td>
<td>Acute onset, scleroderma renal crisis, cancer</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>Ro/SS-A</td>
<td>70-95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>La/SS-B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune myositis</td>
<td>Histidyl aminoacyl-tRNA synthetase, Jo1</td>
<td>25</td>
<td>Interstitial lung disease, Raynaud phenomenon</td>
</tr>
<tr>
<td></td>
<td>Mi-2 nuclear antigen</td>
<td>5-10</td>
<td>Dermatomyositis, skin rash</td>
</tr>
<tr>
<td></td>
<td>MDA5 (cytoplasmic receptor for viral RNA)</td>
<td>20-35 (Japanese)</td>
<td>Vascular skin lesions, interstitial lung disease, Dermatomyositis, cancer</td>
</tr>
<tr>
<td></td>
<td>TIF1γ nuclear protein</td>
<td>15-20</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>CCP (cyclic citrullinated peptides); various citrullinated proteins</td>
<td>60-80</td>
<td>Specific for rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid factor (not specific)</td>
<td>60-70</td>
<td></td>
</tr>
</tbody>
</table>

Listed autoantibodies are associated with high frequencies with particular diseases. *Generic* antinuclear antibodies (ANAs), which may react against many nuclear antigens, are positive in a large fraction of patients with SLE but are also positive in other autoimmune diseases. % positive refers to the approximate % of patients who test positive for each antibody.

The table was compiled with the help of Dr. Antony Rosen, Johns Hopkins University.
Investigations, indirect immunofluorescence

- homogenous
- speckled
- centromeric
- nucleolar

Visit [https://en.wikipedia.org/wiki/Anti-nuclear_antibody](https://en.wikipedia.org/wiki/Anti-nuclear_antibody) for references
Investigations, cont’d

• Antibodies to double-stranded DNA and the so-called Smith (Sm) antigen are virtually diagnostic of SLE

• In addition to ANAs, 30-40% of lupus patients also have autoantibodies against proteins complexed with phospholipids

Plasma proteins:
- prothrombin
- annexin V
- Beta 2-glycoprotein I
- protein S
- Protein C

Its Ab also binds to cardiolipin antigen

Lupus anticoagulant .........?
Risk factors

• Genetic susceptibility...HLA-DQ polymorphisms
  ...inherited deficiencies of C2, C4, or C1q
  ...others

• Environmental factors are more important...UV light and drugs

• Immunological factors:
  - Failure of self-tolerance in B cells
  - CD4+ helper T cells
  - Role of TLRs
  - Role of type I interferons
  - Role of BAFF
Mechanisms

• Systemic lesions...mostly by type III hypersensitivity

• Opsonization of blood cells by autoantibodies

• Antiphospholipid antibody syndrome
Sjogren syndrome

- Most commonly in women between the ages of 50 and 60
- Dry eyes (*keratoconjunctivitis sicca*) and dry mouth (*xerostomia*)
- Primary or secondary
- Lymphocytic infiltration and fibrosis of lacrimal and salivary glands
- Mainly CD4+...and B cells
- 75% are positive for rheumatoid factor
- ANAs in 50-80%
Sjogren syndrome, cont’d

• The most important antibodies are: SS-A & SS-B...90%
  - earlier onset
  - longer disease duration
  - extraglandular manifestations

• HLA association

• Viral infection may be the initial trigger
Sjogren syndrome, cont’d

• Sjogren syndrome-like disease is seen in some patients with AIDS & hepatitis C

• Extraglandular disease in 1/3 of patients
  - synovitis
  - pulmonary fibrosis
  - neuropathy
Sjogren syndrome, cont’d

• Biopsy of the lip
Systemic sclerosis (scleroderma)

- 50s-60s
- M:F 1:3
- Its distinctive features are the striking cutaneous changes, notably skin thickening
Systemic sclerosis (scleroderma), cont’d

• 3 main problems:
  - Inflammation → CD4+...also humoral roles
  - Small blood vessel damage
  - Interstitial and perivascular fibrosis in skin and other tissues

• The majority: also kidney, heart, lung and GI involvement...but late

• Diffuse VS limited scleroderma

Some patients: CREST syndrome
Systemic sclerosis (scleroderma), cont’d

• Raynaud phenomenon...virtually in all patients
  ...precedes other manifestations in 70% of the cases

• Dysphagia is an important symptom...50%

• Nephrotic syndrome is rare

• The most dangerous risk: malignant hypertension
Two ANAs are important in diagnosing systemic sclerosis

1- against DNA topoisomerase I (anti-Scl 70)...highly specific
...10-20% of diffuse disease
...prognostically important

2- anticentromere antibody...20-30%
...more with CREST syndrome
Thank You