Autoimmunity

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Learning Objectives

• Summarize basic concepts of autoimmunity
• Define Systemic Lupus Erythematosus (SLE)
• Summarize health disparities in SLE
• Explain the pathogenesis of SLE
• Given clinical scenarios, recognize the heterogeneity of clinical manifestations of SLE
• Define the American College of Rheumatology (ACR) classification criteria of SLE
• Summarize the key auto-antibodies involved in SLE
• Explain the key manifestations of Sjögren disease, systemic sclerosis and antiphospholipid syndrome

Definition of Autoimmunity

• Normal persons are unresponsive (tolerant) to their own (self) antigens.

• Autoimmunity results from a failure of self-tolerance.

• Immune reactions to self antigens (i.e., autoimmunity)
Definition of Autoimmunity

- Specific immune responses are directed against one particular organ or cell type → localized tissue damage.
- Can be divided into 2 categories:
  1. Organ specific (e.g. Grave’s disease, type 1 DM...)
  2. Systemic (SLE, systemic sclerosis...)

Immunologic Tolerance
Genetic factors in autoimmunity

• Autoimmune diseases have a tendency to run in families, and there is a greater incidence of the same disease in monozygotic than in dizygotic twins.

• Several autoimmune diseases are linked with the HLA locus, especially class II alleles.

Gender Influence

• There is a strong gender bias of autoimmunity
• Women >>>>> Men
• Not well understood
• Hormones?
• Other factors?
Role of Infections and Tissue Injury

Several hypotheses:

• Viruses and other microbes may share cross-reacting epitopes with self antigens

• Microbial infections with resultant tissue necrosis and inflammation

• Many others.....

Systemic Lupus Erythematosus

History

• The word ‘lupus’ is derived from the Latin word for ‘wolf’.

• Named in the 13th century by the physician “Rogerius”.

• He described the rash as erosive facial lesions as a consequence of a wolf’s bite.

• The facial rash is also called “Butterfly rash” because it resembles a butterfly shape.
Definition

- An inflammatory, multisystem, autoimmune disease of unknown etiology with variable clinical and laboratory manifestations and a variable course and prognosis.
- Lupus can be a mild disease, a severe and life-threatening illness, or anything in between.
- The diversity of clinical symptoms in SLE is great, and all organ systems are vulnerable.
- Disease is characterized by periods of flare (when disease is active) and remission (when disease is inactive) and can culminate in irreversible end-organ damage.
- Characterized by a variety of antibodies that are important for diagnosis and responsible for clinical manifestations.

Epidemiology

- Every year there are more than 16,000 new cases of lupus in North America.
- 2–140/100,000 worldwide but as high as 207/100,000.
- Female : male ratio is 9:1.
- 15-45 years old of age.
- Affects minorities (African Americans and Hispanics) more commonly and more severely.

Health disparities in SLE

- Young female.
- Specific racial/ethnic minorities.
- Low income.
- Poverty.
Pathogenesis

Failure to maintain self-tolerance

Autoantibodies formation

Tissue damage

Clinical manifestations of SLE
ACR Classification Criteria

- Malar Rash
- Discoid Rash
- Serositis
- Oral ulcers
- Arthritis
- Photosensitivity
- Blood disorder
- Renal disorder
- DNA
- Immunologic abnormalities
  - (anti-Smith antibody, anti-double stranded DNA, anti-phospholipid antibodies)
- Neurologic symptoms

Mnemonic: SOAP BRAIN MD

Clinical manifestations

- Great masquerader
- Symptoms vary by organ system affected
- Can initially present just with fatigue, rashes, joint achingness

Lupus intangibles

- Fatigue
- Brain fog
- Achiness
- Depression
- Joint pain

Lupus on the outside

- Malar rash
- Raynaud
- Discoid rash
- Sub-acute cutaneous rash

Lupus on the outside

- Alopecia
- Jaccoud deformity
Lupus nephritis

- Immune deposits, which are primarily due to anti-double-stranded DNA antibodies, there is also deposition of IgG, IgA, IgM, C1q and C3.
- The immune deposits in lupus nephritis can occur in the mesangium, sub-endothelial, and/or sub-epithelial compartments of the glomerulus.

Libman-Sacks Endocarditis

- Non-infectious, verrucous thrombi
- Usually on mitral or aortic valve
- Can be associated with anti-phospholipid syndrome

- Remember: LSE in SLE
Subtypes of Lupus

- There are five types:
  1. Systemic lupus erythematosus
  2. Discoid lupus
  3. Drug induced lupus
  4. Neonatal lupus
  5. Overlap syndrome (SLE associated with another AI disease)

Diagnosis of SLE

- A thorough history and physical exam
- Blood work based on pre-test probability

Anti-nuclear antibody (ANA)

- Useful screening test in asymptomatic patients
- Reported as a titer (i.e. 1/160, 1/320, etc....)
- Non-specific but very sensitive (useful when negative)
Other antibodies

<table>
<thead>
<tr>
<th>Antibodies</th>
<th>Specificity for SLE</th>
<th>Clinical associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-DsDNA</td>
<td>High</td>
<td>Lupus nephritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Correlates with disease activity</td>
</tr>
<tr>
<td>Anti-Smith</td>
<td>High</td>
<td>None</td>
</tr>
<tr>
<td>Anti-SSA</td>
<td>Low</td>
<td>Dry eyes/dry mouth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subacute cutaneous Lupus</td>
</tr>
<tr>
<td>Anti-SIB</td>
<td>Low</td>
<td>Same as above</td>
</tr>
<tr>
<td>Anti-RNP</td>
<td>Low</td>
<td>Raynaud, myositis, lung disease</td>
</tr>
<tr>
<td>Anti-phospholipid antibodies</td>
<td>Low</td>
<td>Clotting disorder</td>
</tr>
</tbody>
</table>

Other laboratory tests

- White cell count
- Hemoglobin
- Platelet count
- Creatinine level
- Proteinuria
- Complement 3 and 4
- DsDNA

Treatment of SLE

- NSAIDs
- Anti-malarials
- Corticosteroids
- Immunosuppressive medications
Adjunctive measures

- Avoid sun exposure
- NO smoking
- Healthy diet
- Regular exercise

Mortality in SLE

- Cardiovascular disease: major cause of mortality
- Other factors:
  - High disease severity at diagnosis
  - Younger age at diagnosis
  - Ethnicity: Black, Hispanic, Asian, and Native American populations
  - Male gender
  - Low socioeconomic status
  - Poor patient adherence
  - Poor social support
  - Low education

Clinical case 1

- 20 year old African American female presents to the ED with 3 months of fatigue, joint pain (fingers and wrists), and a rash (picture) that started after she was vacationing in the Caribbean.

1) Which of the following is the most likely diagnosis?
A. Sun burn
B. Rheumatoid arthritis
C. Psoriasis
D. Systemic lupus erythematosus
E. Sjogren’s disease
Clinical case 1

- 20 year-old African American female presents to the ED with 3 months of fatigue, joint pain (fingers and wrists) and a rash (picture) that started after she was vacationing in the Caribbean.

2) Which of the following laboratory screening tests is most appropriate as initial work up?

A. Chest x-ray
B. Lumbar puncture
C. Antinuclear antibody
D. Lyme serology
E. dsDNA

Sjogren’s syndrome

- Autoimmune disease characterized by exocrine glandular dysfunction due to lymphocytic infiltration.
- Female gender
- Can be primary of secondary to another autoimmune disease (RA, SLE...)

Definition
Clinical manifestations

- Dry eyes (xerophthalmia)
- Dry mouth (xerostomia)

But also:
- Vaginal dryness, skin dryness, constipation....
- Parotid enlargement (picture)
- Joint pain

Laboratory abnormalities

- + Anti-SSA and/or anti-SSB antibody
- +Rheumatoid factor
- Renal tubular acidosis (RTA)

Prognosis

- Can cause congenital heart block in newborn of mother with Sjogren. Will need a permanent pacemaker placement.

- Caution: increased risk of lymphoma (40 time increased risk, esp. mucosa-associated lymphoid tissue (MALT))
Clinical case 2

- 65 year old female with 20 year history of Sjogren’s disease comes for follow up. She noticed recent onset of a lump behind her right jaw. Dry eyes and dry mouth are stable.
- Exam: decreased salivary pooling and right parotid gland enlargement.
- Labs: Platelets: 80,000 (were 200,000 a year ago).

Which of the following condition is likely to occur?

A. Sinusitis
B. Parotid gland lymphoma
C. Otitis media
D. Mumps infection

Systemic Sclerosis

- Scleroderma, or systemic sclerosis (SSc), is an autoimmune disease characterized by:
  1) Vasculopathy
  2) Fibrosis
- Significant morbidity and high rates of mortality.

Clinical manifestations

- Raynaud
- Skin tightening (no wrinkles)
- Finger tip ulcers
- Joint contractures
- Renal hypertension
- Dyspnea
- GERD
- Diarrhea/malabsorption
- Weight loss
Definition of Raynaud

- Decreased blood flow to the skin secondary to arteriolar vasospasm in reaction to cold or stress (emotion).

- Color change:
  - White (ischemia) → blue (hypoxia) → red (reperfusion)

- Two types:
  1. Raynaud disease: when primary/idiopathic
  2. Raynaud phenomenon: when associated with another autoimmune disease (e.g., Scleroderma, SLE, Mixed connective tissue disease ...)

  Treatment: vasodilators such as calcium channel blockers.

Subtypes of SSc

1. Diffuse Scleroderma:
   - Extensive skin involvement
   - Interstitial lung disease
   - Anti-topoisomerase I (Scl70)

2. Limited scleroderma: CREST syndrome
   - Limited skin involvement (fingers and face)
   - Calcinosis, Raynaud, Esophageal dysmotility, Sclerodactyly and Telangiectasia
   - Pulmonary hypertension
   - Anti-centromere antibody

Clinical manifestations

- Raynaud
- Sclerodactyly
- Calcinosis
- Telangiectasia

http://www.rheumatology.org/Learning-Center/Educational-Activities/Rheumatology-Image-Library
Clinical case 3

• 36 year old female presents with 6 months of skin tightening, GERD, change in the color of her fingers.
• On physical exam, her BP is 190/100, HR 80, RR 16, T 98, sclerodactyly and few telangiectasia on her face.

1) What process is most likely to explain the cause of her hypertension?
   A. Atherosclerosis
   B. Hyperaldosteronism
   C. Cocaine use
   D. Licorice use
   E. Scleroderma renal crisis

Clinical case 3 (continued)

2) What antibody has been shown to be associated with this condition?
   A. Anti-SSA
   B. Anti-topoisomerase (anti-Scl70)
   C. Anti-RNA polymerase III
   D. Anti-centromere antibody
   E. Anti-nuclear antibody
Anti-phospholipid syndrome

• Can be primary or secondary (most commonly associated with SLE)

• Diagnosis is based on a clinical event of thrombosis (arterial or venous) or a pregnancy morbidity along with abnormal laboratory test (clotting antibody).

Anti-phospholipid antibodies

• Anticardiolipin antibodies (aCL)

• Anti-beta2-Glycoprotein I antibodies

• Lupus anticoagulant (LAC)

  PS: Can cause false positive VDRL/RPR test. LAC can prolong PTT.

Take home points

• Autoimmune diseases are the result of a dysregulated immune system

• SLE diagnosis is often very challenging and often delayed because of the myriad of symptoms it can present with

• ANA is sensitive but NOT specific, remember your pre-test probability

• DsDNA and complement 3 and 4 can be used to monitor disease activity

• Sjogren disease reflects exocrine gland dysfunction. Monitor for lymphoma transformation

• Systemic sclerosis can be limited or diffuse

• Mortality from SSc is often related to pulmonary complications
Thank you!
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