The Immune System and Immune Mediated Diseases
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Reading:  Big Robbins Chapter 6
Robbins Basic Pathology pp 110-159

Lab tests:  Pages correspond to Bakeman’s ABC’s of Interpretive Lab Data
HLA testing:  pg. 315
Markers of Inflammation:  Acute Phase Reactants  pg. 11
Erythrocyte sedimentation Rate pg.228
C-reactive Protein  pg. 186
Antinuclear Antibody:  pg. 67
Connective Tissue Disease:  pgs. 173-178
HIV testing:  pgs. 308-313

Online: Case 16, Mr. Conrad’s nosebleed.
Outline:

1. Review of Hypersensitivity Reactions
2. Systemic Autoimmune Diseases
   a. Tolerance and mechanisms of autoimmunity
   b. Autoantibodies
   c. Systemic Lupus Erythematosus
   d. Sjogren Syndrome
   e. Systemic Sclerosis
   f. Inflammatory myopathies
   g. Mixed connective tissue disease

3. Pathology of Transplantation
   a. Mechanisms of rejection
   b. Morphologic features of rejection
   c. Increasing graft survival
   d. Graft versus host disease
   e. Other complications.

4. Laboratory Assessment of Immune Status

5. Immunodeficiency: Congenital and Acquired
   a. Acquired versus congenital immunodeficiencies
   b. Clinical manifestations of congenital immunodeficiencies
   c. Selected Congenital Immunodeficiencies
      X-linked agammaglobulinemia (Bruton's)
      Common Variable Immunodeficiency
      IgA Deficiency
      Hyper IgM Syndrome
      Thymic hypoplasia (DiGeorge Syndrome)
      Severe Combined Immunodeficiency (SCID)
      Wiskott-Aldrich Syndrome
   
   d. Acquired Immunodeficiency
      Pathology and Pathogenesis of HIV Infection

6. Amyloidosis

Reading: Robbins Basic Pathology pp 110-120 (review-hypersensitivity), 120-159 (new)
Autoimmunity and Autoimmune Disease

Tolerance and Mechanisms of Autoimmunity

Mechanisms of Immunologic *Tolerance*

Central:

Peripheral:

Mechanisms of *Autoimmunity*

Barriers to intrathymic deletion

Genetic factors and "suseceptibility genes"

Infections and Autoimmunity

Tissue injury (UV light)

Other factors

*Autoantibodies*

Role in autoimmune disease:
1)
2)
3)
4)
Antinuclear Antibodies

Definition:

Detection of ANA: Immunoassay (automated) versus indirect immunofluorescence.

ANA: patterns of immunofluorescence:

1) 
2) 
3) 
4) 

Systemic Autoimmune Diseases

Tests for systemic inflammation:

C-reactive protein

Erythrocyte sedimentation rate (ESR or Sed rate)

Systemic Lupus Erythematosus

*Defining:* multisystem, variable signs/symptoms and clinical course

Diagnostic criteria (Revised Criteria)

*Demographics*

Prevalence:
Sex:
Age:
Race:

*Pathogenesis*
Genetic factors
1) 
2)
Environmental factors
1) 
2) 
3) 
4) 
5) 

Immune system abnormalities
1) 
2) 
3) 

**Autoantibodies**

Antinuclear antibodies:

Antiphospholipid antibodies:

Other autoantibodies:

**Mechanism of tissue injury:**
1) 
2) 
3)
Pathology of Systemic Lupus Erythematosus

Blood vessels:

Kidneys:

Glomerulonephritis: (Class I-VI)

Skin:

Joints:

Central nervous system:

Cardiovascular:

Other:
  Lungs
  Liver
  Spleen

Presentation and clinical course

Treatment

Mild- Moderate disease:

Severe disease:

Survival

Variants of Lupus:

Discoid lupus

Drug Induced
Sjogren Syndrome

**Definition:**
1) 
2) 
3) 

Primary versus Secondary

**Clinical presentation**

**Pathogenesis:**

Cellular and Humoral mechanisms

**Laboratory findings:**

ANA

Rheumatoid factor (RF)

**Pathologic features:**

1) 
2) 
3) 

**Multisystem disease**

Extraglandular involvement occurs in ____ %

Examples:
1) 
2) 
3) 
4)
Systemic Sclerosis (Scleroderma)

**Definition:**

**Prevalence:**

Diffuse scleroderma:

Localized scleroderma:

C R E S T

**Etiology/Pathogenesis:**

Endothelial cell injury

Immune activation

Fibrogenic cytokines

Autoantibodies:

1)

2)

**Pathologic features:**

Skin

GI tract

Kidney

Lungs

Heart
**Presentation and Clinical Course**

Raynaud phenomenon

Skin changes

Visceral involvement and associated symptoms

**Treatment:**

**Prognosis/Survival:**

**Other Autoimmune Disorders:**

**Inflammatory Myopathies**

Dermatomyositis

Polymyositis

Associated autoantibody:

**Mixed Connective Tissue Disease**

Definition

Associated autoantibody:
Pathology of Transplantation

Current Scope

Mechanisms of Transplant (allograft) Rejection

Antigen recognition: direct versus indirect

Cell mediated rejection:

Antibody mediated rejection:

Morphology:
Depends on time frame

Hyperacute

Acute

Chronic
Methods of Improving Graft Survival

Compatibility:

ABO

HLA antigens

Immunosuppressive Therapy:

1) 
2) 
3) 
4) 
5) 
6)

NEJM Vol 351; 26 Dec 2004

Other factors to consider:

Bone Marrow Transplantation (Hematopoietic Stem Cells)

Graft versus Host Disease

Pathogenesis

Acute GVHD

Chronic GVHD

Treatment
Other Complications of Transplantation

Opportunistic infections

Post Transplant Lymphoproliferative Disorders (PTLD)

Laboratory Assessment of Immune Status

Testing of Humoral Immunity:

1) 

2) 

Testing of Lymphocyte Number and Function:

1) 

2) 

3) 

In Vivo Testing of Immune Function

Testing of Innate Immunity

Neutrophils:
Number and Function

NBT test:

Complement:
Total
Components
Immunodeficiency: Congenital and Acquired

Acquired versus Congenital Immunodeficiencies

1)

2)

**Congenital Immunodeficiencies**

Clinical Manifestations of Congenital Immunodeficiencies

Infections

T cell defects:

B cell defects:

Granulocytes:

Complement:

Time frame:

Other manifestations:

1)

2)
Selected Congenital Immunodeficiencies:

*Disease with abnormal Immunoglobulin Production*

X-linked (Bruton's) Agammaglobulinemia

Incidence:

Clinical features:
1)

2)

3)

Molecular defect:

Other manifestations:

Treatment:

**Common Variable Immunodeficiency (CVID)**

Incidence:

Clinical features:
1)

2)

Molecular defect:

Other manifestations:

**Isolated IgA Deficiency**

Incidence:

Clinical features:
1)

2)
Molecular defect

Other manifestations

**Hyper-IgM Syndrome**

Incidence:

Clinical features:
1) 
2) 

Molecular defect:

Other manifestations:

*Diseases with predominantly T cell abnormalities*

**Severe Combined Immunodeficiency (SCID)**

Incidence:

Clinical features:
1) 
2) 
3) 

Inheritance

Molecular defects:
1) 
2) 
3) 

Treatment (retroviral gene transfer, BM transplantation)
Other Congenital Syndromes:

DiGeorge Syndrome (22q11 deletion syndrome)
C
A
T
C
H
22

Wiskott-Aldrich Syndrome:
Triad:
1)
2)
3)

Inheritance
Molecular defect

Other manifestations:

Deficiencies of Innate Immunity

Complement deficiencies
1)
2)
3)

Neutrophil Deficiency

Chronic Granulomatous Disease (CGD)
Acquired Immunodeficiency: Pathology and Pathogenesis of HIV Infection

Epidemiology

Worldwide distribution of HIV Infection

Risk Groups:

Men who have Sex with Men (MSM)

Intravenous Drug Users

Heterosexual contacts of high risk groups

Blood and Blood-product recipients

Hemophiliacs

Children born to HIV infected women (vertical transmission)

Mode of Transmission

Sexual

Parenteral

Mother-to-Infant

Virology

HIV 1 and HIV 2

Viral structure
Pathogenesis of Infection

T Cell Destruction

Kumar et al: Robbins Basic Pathology, 9e. Copyright © 2013 by Saunders, an imprint of Elsevier Inc.
Immunologic Consequences of T Cell Loss

Macrophages and Dendritic Cells and HIV

CNS Involvement by HIV

Clinical and Immunologic features of Natural History of HIV Infection

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Clinicopathologic Features of AIDS

"Acute HIV" Illness

HIV associated Lymphadenopathy

HIV and Lymphomas

Kaposi’s Sarcoma

Cervical and Anal HPV-mediated Neoplasia

Central Nervous system

1) 
2) 
3) 
4) 

Infections

Bacterial/Mycobacterial

Community acquired bacterial infection

Mycobacterium tuberculosis and Atypical mycobacteria
Fungal and Protozoal

Candida albicans
Pneumocystis jeroveci
Histoplasma capsulatum
Cryptococcus neoformans
Cryptosporidium
Toxoplasma gondii

Viral

Cytomegalovirus
Herpes simplex
Epstein Barr Virus
JC Virus

Laboratory Testing in HIV Infection

Diagnosis:
Enzyme Linked Immunosorbant Assay (ELISA)
Western Blot (confirmatory)
P24 antigen testing
PCR for HIV RNA/DNA

Monitoring Disease Progression and Prognosis:
HIV mRNA by PCR
CD4 lymphocyte Quantitation

Tailoring Drug Therapy/Detecting Resistance:
HIV genotyping
Amyloidosis

**Definition:**

Characteristics of Amyloid

**Pathogenesis:**

A disorder of abnormal protein Folding.

*AL amyloid*

*AA amyloid*

*Aβ amyloid*

*Transthyretin*

*β2 microglobulin*

*Endocrine sources*
Pathology of Amyloidosis:

Clinical Presentation and Diagnosis

Treatment and Prognosis
Immunopathology Study Questions

Transplantation:
1. What is the difference between direct and indirect allograft recognition?
2. In acute rejection of the kidney, what pathologic change typifies cellular rejection? Antibody-mediated rejection?
3. What antigen system(s) are most important in graft rejection?
4. How does HLA mismatch affect the probability of Graft vs Host disease (GVHD)?
5. What major organ systems are affected by GVHD?
6. Post transplant lymphoproliferative disorder is associated with what viral pathogen?

Autoimmunity
1. What are the major clinical signs and symptoms of systemic lupus (SLE)?
2. What is a wire loop lesion?
3. What is the significance of a positive ANA in an asymptomatic individual?
4. What specific autoantibodies are helpful in the diagnosis of SLE?
5. How do discoid and drug-associated lupus differ from SLE?
6. Based on current knowledge, what main mechanisms are involved in immunologic tolerance?
7. Lupus is latin for __________?
8. What is the antiphospholipid antibody syndrome? What is the relationship of APS to lupus?
9. Give an example of each of 3 different types of hypersensitivity reactions occurring in SLE.
10. Fibrous tissue deposition occurs most commonly in which organs in progressive systemic sclerosis (scleroderma, PSS)?
11. What is the pathogenesis of PSS?
12. What specific autoantibody(ies) is/are helpful in diagnosis of PSS? CREST?
13. What does CREST stand for?
14. True or False. Some patients can have spontaneous softening of their dermal sclerosis after years of disease.
15. What severe complication can be seen in PSS associated renal disease?
16. What is Raynaud’s phenomenon?
17. What is sicca syndrome?
18. Sjogren’s syndrome is most commonly associated with what other autoimmune disease?
19. What specific autoantibody(ies) is/are helpful in the diagnosis of Sjogren syndrome?
20. Anti-Jo and Anti-La are associated with what autoimmune disease (es)
21. How do dermatomyositis and polymyositis differ in terms of the target of the inflammatory process?
22. Patients with mixed connective tissue disease commonly have what autoantibody?
23. What is the genetic basis for Bruton’s agammaglobulinemia?
24. What infections are commonly associated with B cell deficiencies? T cell deficiencies?
25. Adenosine deaminase deficiency and Jak 3 mutations are associated with what congenital immunodeficiency?
26. What immunodeficiency is associated with anaphylactic reaction to transfusion of plasma-containing products?
27. The triad of eczema, thrombocytopenia, and recurrent infections is seen in what congenital immunodeficiency?
28. Which inherited immunodeficiency syndrome is associated with hypocalcemia?
29. What risk group has shown the greatest increase in proportion of new HIV infection over the last decade in the US?
30. What are major determinants of sexual transmission of HIV?
31. What are major determinants of perinatal transmission of HIV?
32. What is the significance of the LTR (long terminal repeat) region of the HIV genome?
33. How do CD 4 cells and macrophages bind HIV? How do they differ in terms of their interaction with the virus?
34. How is B cell function affected by HIV disease?
35. HIV is an a. RNA b. DNA virus?
36. How do CD4 count and Viral RNA quantitation (viral load) differ in terms of their clinical significance?
37. What are the “co-receptors” involved in HIV binding and entry?
38. Where does HIV virus reside during the clinical “latent” period?
39. How does HIV gain access to the central nervous system?
40. List several important mechanisms for T cell destruction in the course of HIV infection
41. How do the ELISA and Western Blot assays differ in terms of their role in diagnosis of HIV infection? What are causes of false positive ELISAs?
42. What is the pathogenesis of kaposi’s sarcoma?
43. What happens to the lymphoid tissues during the course of HIV/AIDS?
44. What malignancies are seen in higher frequencies in patients with HIV infection?
45. What is PML?
46. What are the most common clinical manifestations of the following opportunistic pathogens in the setting of HIV infection?
   a. Cryptococcus neoformans
   b. Pneumocystis carinii
   c. M. tuberculosis and M. avium complex
   d. Histoplasma capsulatum
   e. Toxoplasmosis
   f. JC virus
47. What type of amyloid protein is associated with each of the following?
   a. Plasma cell dyscrasias
   b. Systemic infection/inflammatory disorder
   c. Alzheimer’s disease
   d. Medullary thyroid carcinoma
48. What special stain is used to identify amyloid on tissue biopsies?
49. What tissues are most commonly affected in systemic amyloidosis?