3. Autoimmunity

I. Introduction

A. Introduction

1. Normal individuals do not produce destructive immune responses to their own tissues due to “immune tolerance.

   a. Self-recognition of all body components.

   b. Host tolerates self antigens because an immune reaction directed against itself would injure the host, an undesired effect.

2. Autoimmune response.

   a. Auto-antibody directed against a “self” antigen.

   b. Considered abnormal but usually does not results in disease.

   c. May occur in healthy individuals.

3. Autoimmune disease

   a. Disorder in which tissue injury is caused by an immunologic reaction of the host to his own tissues.

   b. Precise mechanisms that initiate autoimmune diseases are not known.

   c. Can be classified as systemic or organ specific, frequently have overlap.

B. Possible proposed mechanisms involved in autoimmune disease.

1. Forbidden Clone Theory

   a. A clone of changed or altered lymphocytes arises through mutation.

   b. These cells lack foreign surface antigens and are not destroyed by the host.

   c. Because of alteration may recognize host as foreign.

2. Altered Antigen Theory

   a. Surface antigens on host altered by chemical, biological or physical means.

   b. This new antigenic determinant may be recognized as foreign by the host.
3. Sequestered Antigen Theory
   a. Some antigens in the body are hidden from cells of the immune system.
   b. If there is damage to these organs causing exposure of these sequestered antigens an immune reaction may occur

4. Immunologic Deficiency Theory
   a. Relates the increased frequency of autoantibodies and increased immune system deficiency to age.
   b. Mutation or loss of immune regulatory powers results in the condition in which self antigens behave as foreign antigens.

5. Genetic influence
   a. It is well recognized that certain immune disorders predominate in females and in families.
   b. Determined by family studies.
   c. Genetic links have occurred between diseases and HLA antigens

C. Contributing Factors of Autoimmunity
   1. Defects in the immune system.
   2. Influence of hormones
   3. Environmental conditions

D. Classification of Autoimmune Diseases
   1. Systemic
   2. Organ specific
   3. Both

II. Systemic Lupus Erythematosus - http://www.lupus.org/
   A. Introduction
      1. Chronic, systemic, inflammatory disease caused by immune complex formations.
      2. Pathophysiology associated with clinical features secondary to immune complexes depositing in tissues resulting in inflammation.
3. Peak age of onset is 20 to 40 years of age.
4. Found more frequently in women.
5. Has both genetic and environmental factors.

B. Clinical Signs

1. Extremely diverse and nonspecific.
2. Joint involvement most frequent sign: polyarthralgia and arthritis occur in 90% of patients.
3. Skin manifestations next most common.
   a. Erythematous rash may appear.
   b. Most classic is butterfly rash.
4. Renal involvement very common.
   a. Caused by deposition of immune complexes in kidney tissue.
   b. Leads to renal failure, most common cause of death.
5. Other systemic effects:
   a. Cardiac
   b. Central nervous system.
   c. Hematologic abnormalities.

C. Immunologic Findings

1. Lupus Erythematosus (LE) cell, neutrophil which has engulfed the antibody-coated nucleus of another cell.
   a. First classic test to aid in diagnosis.
   b. Not utilized anymore, may still see in older references.
2. Over activity of B cells main immunologic characteristic.
   a. Antinuclear antibodies produced.
   b. More than 28 antibodies associated with LE have been identified.
   c. Level of antibody production correlates with severity of symptoms.
   d. Estrogen enhance B cell activation.
3. Decrease in absolute number of T cells
4. Accumulation of immune complexes with activation of complement lead to kidney damage.

5. Drug induced lupus may occur, discontinue drug, symptoms usually disappear.

D. Laboratory Diagnosis

1. Screening test for **anti-nuclear antibodies** (ANA) first test done.
   
a. Antibodies directed against nuclear material of cells.

b. Fluorescent anti-nuclear antibody (FANA) most widely used, extremely sensitive, low diagnostic specificity.
   
   1) Animal or human cells fixed to slide.
   2) Add patient serum and incubate.
   3) Wash to remove unreacted antibody.
   4) Add anti-human globulin labeled with fluorescent tag or enzyme.

c. Patterns of reactivity [http://www.scimedx.com/anaifa.htm]:
   
   1) Homogenous-entire nucleus stained
   2) Peripheral-rim of nucleus stained
   3) Speckled-spots of stain throughout nucleus
   4) Nucleolar-nucleolus only stained

d. False positives and negatives occur.

e. If positive, perform profile testing.

5. Anti-nuclear antibodies detected by FANA - [http://www.aruplab.com/guides/clt/tests/clt_a-57.htm]

   a. Double-stranded DNA (ds-DNA) antibodies are most specific for SLE, correlate well with disease activity.

   b. Antihistone antibody second major antibody found in SLE.

   c. Deoxyribonucleoprotein (DNP) antibody, responsible for LE cell phenomena and available as a latex agglutination test.

   d. Anti-Sm antibody, specific for LE.

   e. SS-A/Ro and SS-B/La antibodies, most common in patients with cutaneous manifestations.

   f. Anti-nRNP detected in patients with SLE as well as mixed connective tissue disease.
3. Autoimmunity

6. Anti-nuclear antibodies detected by immunodiffusion.
   a. Used to determine specificity.
   b. Ouchterlony double diffusion most frequently used to identify antibodies to: Sm, nRNP, SS-A/Ro, SS-B/La and others.
   c. Test is not as sensitive but very specific.

7. Antiphospholipid antibodies may be present and are of two types.
   a. Anticardiolipin.
   b. Lupus anticoagulant, if present, may cause spontaneous abortion and increase risk of clotting, platelet function may be affected.

E. Treatment

1. Aspirin and anti-inflammatories for fever and arthritis.

2. Skin manifestations-anti-malarials or topical steroids.

3. Systemic corticosteroids for acute fulminant lupus, lupus nephritis or central nervous system complications.

4. Five year survival rate is 80 to 90%.


A. Introduction

1. Chronic inflammatory disease primarily affecting the joints, but can affect heart, lung and blood vessels.

2. Women three more times as likely as men to have it.

3. Typically strikes at ages between 20 and 40, but can occur at any age.

4. Progress of disease varies.
B. Clinical Signs

1. Diagnosis based on criteria established by American College of Rheumatologists, must have at least 4 of the following:
   a. Morning stiffness lasting 1 hour.
   b. Swelling of soft tissue around 3 or more joints.
   c. Swelling of hand/wrist joints.
   d. Symmetric arthritis.
   e. Subcutaneous nodules
   f. Positive test for rheumatoid factor.
   g. Xray evidence of joint erosion.

   a. Morning stiffness and joint pain improve during the day.
   b. Symmetric joint pain: knees, hips, elbows, shoulders.
   c. Joint pain leads to muscle spasm, limits range of motion, results in deformity.

3. Approximately 25% of patients have nodules over bones (necrotic areas), nodules can also be found in organs.

4. Certain bacteria may trigger RA due to certain proteins that possess antigens similar to those antigens found in joint, ie, molecular mimicry

C. Immunologic Findings

1. **Rheumatoid Factor** (RF) is an IgM antibody directed against the Fc portion of the IgG molecule, it is an anti-antibody.

2. Not specific for RA, found in other diseases.

3. Immune complexes form and activate complement and the inflammatory response.

4. Enzymatic destruction of cartilage is followed by abnormal growth of synovial cells, results in the formation of a pannus layer.

D. Laboratory Diagnosis

1. Diagnosis is based on:
   a. Clinical findings.
   b. Radiographic findings
   c. Laboratory testing.

2. Laboratory tests involve testing patients serum with red blood cells or latex particles coated with IgG, agglutination is a positive result.
3.  Nephelometry and ELISA techniques are available to quantitate the RF.

4.  Erythrocyte Sedimentation Rate (ESR) used to monitor inflammation.

5.  C-Reactive protein (CRP) is utilized to monitor inflammation
   a.  Produced in response to inflammation and necrosis.
   b.  Latex particles are coated with anti-CRP and mixed with patient serum.
   c.  Agglutination indicates presence of CRP.
   d.  Postzone reactions are common, test is performed on both undiluted and diluted serum samples.
   e.  CRP is better than ESR because:
       1)  It is not affected by anemia or abnormal serum proteins.
       2)  It rises faster during inflammation and returns to normal rapidly after inflammation subsides.
   f.  Presence of CRP is not diagnostic, present in other conditions.

3.  Test for complement and other autoantibodies will help rule out other diseases.

E.  Treatment

1.  Rest and nonsteroidal anti-inflammatory drugs control swelling and pain.

2.  Substantial functional loss seen in 50% of patients within 5 years.

3.  Slow acting antirheumatic drugs are coming into use but have side affects.


IV.  Hashimoto’s Thyroiditis - http://www.thyroidmanager.org/Chapter8/8-contents.htm

A.  Introduction

1.  Organ specific disease affecting the thyroid gland.

2.  Most often seen in women 30 to 40 years old, may be genetic predisposition.

3.  Common cause of hypothyroidism.

4.  Causes diffuse hyperplasia in the gland resulting in development of a goiter.

5.  Thyroid autoantibodies are formed.

B.  Laboratory Testing

1.  Antithyroglobulin antibodies found in 80%, is not diagnostic.
2. Levels of antibody associated with severity of disease.

C. Treatment

1. Thyroid hormone replacement.
2. Spontaneous remissions have occurred.

V. Graves’ Disease - thyrotoxicosis - http://www.thyroid.ca/Guides/HG06.html

A. Introduction

1. Characterized by hypothyroidism.
2. Women more susceptible, occurs most frequently between 30 and 40 years of age.
3. Genetic link suspected.

B. Clinical Signs

1. Goiter is soft instead of rubbery.
2. Symptoms: nervousness, insomnia, depression, weight loss, heat intolerance, breathlessness, fatigue, cardiac dysrhythmias, and restlessness.
3. Exophthalmus, bulging of eyeballs from socket.

C. Laboratory Diagnosis

1. Presence of thyroid-stimulating hormone receptor antibody, causes release of thyroid hormones.
2. Key findings are elevated total and free T3 (triiodothyronine) and T4 (thyroxine), the thyroid hormones.
3. Thyroid stimulating hormone (TSH) is reduced due to antibody stimulation of the thyroid.

D. Treatment

1. Medication.
2. Radioiodine therapy to destroy the thyroid.
3. Surgery
VI. Insulin Dependent Diabetes Mellitus (IDDM) -

A. Introduction

1. Autoimmune process causes destruction of cells in the pancreas resulting in insufficient insulin production.

2. Occurs before age 20, peak onset between 10 and 14 years.

3. Inherited susceptibility.

4. Environmental influences include possibility of viral infections.

B. Complications

1. With its complications, diabetes is the seventh leading cause of death in the United States.

2. Diabetes is the leading cause of new blindness in people 20-74 years of age.

3. Ten to twenty-one percent of all people with diabetes develop kidney disease.

4. People with diabetes are 2-4 times more likely to have heart disease.

5. About 60%-70% of people with diabetes have mild to severe forms of diabetic nerve damage, which, in severe forms, can lead to lower limb amputations.

C. Laboratory Testing.

1. The American Diabetes Association (ADA) recommendations for diagnosing diabetes state that patients be told they have diabetes if any of the criteria below applies:
   a. Fasting plasma glucose is above 126 mg/dl;
   b. Diabetes symptoms exist and casual plasma glucose is equal to or above 200 mg/dl; or
   c. Plasma glucose is equal to or above 200 mg/dl during an oral glucose tolerance test.

2. The ADA now also recommends that all individuals age 45 and above be tested for diabetes, and if the test is normal, they should be re-tested every three years.

3. Testing should be conducted at earlier ages and carried out more frequently in individuals who are any of the following:
   a. obese;
   b. have a first degree relative with diabetes;
   c. are members of a high-risk ethnic population (African-American, Hispanic, Native American, Asian);
   d. have delivered a baby weighing more than 9 pounds;
e. have had gestational diabetes;
f. are hypertensive;
g. have HDL cholesterol levels equal to or less than 35 mg/dl or triglyceride levels equal to or greater than 250 mg/dl;
h. or who, on previous testing had impaired glucose tolerance or impaired fasting glucose.

4. If genetic predisposition is suspected perform testing to detect antibodies to pancreatic islet cells.

5. Antibodies to insulin detected by RIA or ELISA methods.

C. Treatment

1. Injected insulin.

2. Immunosuppressive drugs for newly diagnosed patients.

VII. Other Diseases

A. Multiple sclerosis - [http://medlib.med.utah.edu/kw/ms/lectures.html](http://medlib.med.utah.edu/kw/ms/lectures.html)

1. Destruction of myelin sheath of axons results in formation of lesions (plaques) in white matter of brain and spinal cord.

2. Cause may include genetic and environmental factors.

3. Damage to CNS cause visual disturbances, weakness in extremities, locomotor incoordination and numerous sensory abnormalities.

4. Most often seen between ages of 20 and 50.

5. Increase in immunoglobulins in spinal fluid is seen.

6. RIA used for antibody detection.


1. Symptoms: facial weakness, difficulty chewing and swallowing, and inability to maintain support of trunk, neck or head.

2. Antibody mediated damage to acetylcholine receptors in skeletal muscles leading to progressive muscle weakness.

   a. Acetylcholine released from nerve endings to generate muscle contraction.
b. Antibody combines with receptor site, blocking acetylcholine binding.
c. Receptors destroyed by action of antibody and complement.

3. Symptoms aggravated by increased muscle use.
4. Associated with presence of other autoimmune diseases.

C. Goodpasture’s Syndrome - [http://www.outlinemed.com/demo/nephrol/12390.htm](http://www.outlinemed.com/demo/nephrol/12390.htm)
   1. Antibodies react with antigens in the glomerular basement membrane of the kidney, results in severe necrosis.
   2. Antigen in kidney is similar to antigen found in lungs, resulting in antibody reacting with lung tissue resulting in pulmonary hemorrhage.
   3. Specific anti-basement antibodies can be demonstrated.

D. Sjogren’s Syndrome - [http://www.sjogrens.org/](http://www.sjogrens.org/)
   1. Most often occurs secondary to RA, SLE or other autoimmune disorders
   2. Dry eyes and mouth due to damage to secretory ducts.
   3. ANA and RF positive
   4. 90% of cases found in women.

E. And Scleroderma - [http://www.sclero.org](http://www.sclero.org)
   1. Fibrosis of connective tissue
   2. Most frequently found in females ages 20-60 years old.
   3. Progressive systemic sclerosis
   4. CREST syndrome
      a. calcinosis
      b. Raynoud’s
      c. Esophageal dysmotility
      d. Sclerodactyly
      e. Telangiectases
VIII. Immunoproliferative Disease

A. Introduction

1. Introduction
   a. Malignant and pre-malignant proliferation of cells.
   b. Broadly classified as leukemias and lymphomas.

2. B-cell immunoproliferative disorders most commonly evaluated.
   a. B-cell lineage develop into plasma cells
   b. Urine antibodies used to diagnose and evaluate certain B-cell proliferations
   c. B-cells produce one antibody specificity (monoclonal).
   d. Persistent presence of large amounts of a single immunoglobulin suggests malignancy.
   e. Increase in total amount of one specific clone characteristic of benign reactive immunoproliferative disease.

B. Plasma Cell Dyscrasias

1. Include several related syndromes:
   a. Multiple myeloma
   b. Waldenstrom’s macroglobulinemia
   c. Light-chain disease
   d. Heavy-chain disease
   e. Monoclonal gammopathy of undetermined significance.

2. Characteristic is over production of a single immunoglobulin component.
   a. Paraprotein or myeloma protein.
   b. Diagnosis and monitoring dependent on detecting and quantitating the paraprotein.
   c. Screening and confirmatory tests performed in most clinical laboratories.

C. Multiple Myeloma - http://cancernet.nci.nih.gov/wyntk_pubs/myeloma.htm

1. Malignancy of mature plasma cells.
   a. Most serious and common of plasma cell dyscrasias.
3. Autoimmunity

b. Age of diagnosis 40 to 70 years, found in blacks twice as frequently as whites, and men twice as likely as women.

c. Have excess of plasma cells in the bone marrow.

d. Level of normal immunoglobulin decreased in proportion to abnormal immunoglobulin.

2. Immunoglobulin produced by malignant clone, can be of any class, IgG most common.

3. Important diagnostic feature is presence of Bence Jones protein in the urine.

a. Abnormal production of free immunoglobulin light chains, kappa or lambda.

b. Can be detected by immunoelectrophoresis or heat precipitation.

4. Clinical manifestations:

a. Hematologic related to failure of bone marrow to produce normal number of hematopoietic cells, leads to anemia, thrombocytopenia and neutropenia.

b. High levels of immunoglobulins lead to rouleaux formation being noted on blood smear.

c. High levels of abnormal plasma cells leads to deficiency in normal immunoglobulin levels.

d. Myeloma involves bone leading to lytic lesions, bone pain and fractures.

e. Deposition of antibody derived material leads to organ dysfunctions, with kidneys most commonly involved.

f. Hyperviscosity develops when protein levels are high, especially with IgM producing tumors.

g. Hemorrhage can occur due to thrombocytopenia and paraprotein interferes in normal hemostasis.

D. Waldenstrom’s Macroglobulinemia - http://www.iwmf.com/

1. Malignant proliferation of IgM producing lymphocytes

a. Malignant cells more immature than plasma cells, with appearance being between small lymph and plasma cell.

b. Plasmaclayoid lymphs infiltrate bone marrow, spleen and lymph nodes.
2. Some IgM paraproteins behave as cryoglobulins, precipitate at cold temperatures.
   a. Occlude small vessels in patient’s extremities in cold weather.
   b. Leads to skin sores and necrosis of fingers and toes.

3. Cryoglobulins detected in blood or plasma by placing the sample in a refrigerator in the clinical laboratory.
   a. Precipitate forms at low temperatures.
   b. Dissolves upon rewarming.
   c. May be associated with a cold red cell autoantibody directed against the I antigen on the patient’s own red blood cells, may result in hemolytic anemia.

4. Patients with stable production of monoclonal IgM without infiltration of marrow or lymphoid tissue are considered to have cold agglutinin syndrome.

5. Clinical symptoms:
   a. Anemia
   b. Bleeding
   c. Hyperviscosity

6. Median survival 5 years versus multiple myeloma, 3 years.

E. Laboratory Diagnosis

1. Measurement of immunoglobulin levels in serum.

2. Serum protein electrophoresis to separate and detect abnormal levels, myelomas which produce only light chains may be missed.

3. Immunoelectrophoresis used to evaluate monoclonal gammopathies detected by SPE.

4. Immunofixation electrophoresis also used to evaluate monoclonal gammopathies.

5. Serum viscosity measurements useful for Waldenstrom’s macroglobulinemia or high levels of IgG or IgA paraproteins.

6. Bone marrow biopsy to establish diagnosis of lymphoproliferative disorder and determine extent of bone marrow replacement by malignancy.