PATHOLOGY

MD3

PATHOLOGY

Immunopathology

Immunopathology

Learning Objectives

- ❑ Explain information related to hypersensitivity reactions and autoimmune diseases
- ❑ Answer questions about primary/secondary immune deficiency syndromes
- ❑ Demonstrate understanding of AIDS
- ❑ Answer questions about immunology of transplant rejection

Immunopathology

HYPERSENSITIVITY REACTIONS

Immunopathology

Type I (immediate) hypersensitivity

Type I (immediate) hypersensitivity reactions **(anaphylactic type)** are characterized by IgE-dependent release of chemical mediators from mast cells and basophils.

Cross-linking of IgE bound to antigen to IgE Fc receptors on the surface of mast cells and basophils causes degranulation. This binding triggers release of chemical mediators that include histamine and heparin; eosinophil chemotactic factor; leukotriene B4 and neutrophil chemotactic factor; and prostaglandin D4, platelet-activating factor (PAF), and leukotrienes C4 and D4. Influx of eosinophils amplifies and perpetuates the reaction. Effects may be systemic (anaphylaxis, as for example due to bee stings or drugs) or localized (food allergies, atopy, and asthma).

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Type II hypersensitivity reactions (antibody-mediated)

Type II hypersensitivity reactions (antibody-mediated) are mediated by IgG or IgM antibodies directed against a specific target cell or tissue. Reactions can take several forms.

- In complement-dependent cytotoxicity, fixation of complement results in osmotic lysis or opsonization of antibody-coated cells; examples include autoimmune hemolytic anemia, transfusion reactions, and erythroblastosis fetalis.
- In antibody-dependent cell-mediated cytotoxicity (ADCC), cytotoxic killing of an antibody-coated cell occurs; an example is pernicious anaemia.
- Antireceptor antibodies can activate or interfere with receptors; examples include Graves disease and myasthenia gravis.

Immunopathology

Type III hypersensitivity

Type III hypersensitivity reactions **(immune complex disease)** are characterized by the formation of in situ or circulating antibody-antigen immune complexes, which deposit in tissue resulting in inflammation and tissue injury.

Examples include

- Serum sickness,
- Systemic lupus erythematosus (SLE), and
- Glomerulonephritis

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Type IV hypersensitivity

Type IV hypersensitivity reactions **(cell-mediated type)** are mediated by sensitized T lymphocytes. In delayed type hypersensitivity, CD4+ TH1 lymphocytes mediate granuloma formation; examples include the PPD skin test and tuberculosis.

In cytotoxic T-cell–mediated hypersensitivity, CD8+ T-cell lymphocytes destroy antigen-containing cells; examples include type 1 diabetes, virus-infected cells, immune reaction to Tumor-associated antigens, and graft rejection.

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Type V hypersensitivity

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AUTOIMMUNE DISEASES

Note

Multiple autoantibodies may be produced and are commonly directed against nuclear antigens (DNA, histones, nonhistone nuclear RNA proteins) and blood cells.

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AUTOIMMUNE DISEASES

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by loss of self-tolerance and production of autoantibodies. Females are affected much more often than males (M:F = 1:9); peak incidence is age 20–45; and African Americans are affected more often than Caucasians.

The mechanism of injury in lupus is a mix of type II and III hypersensitivity reactions.

Important **autoantibodies** that may be detected in the sera from lupus patients include antinuclear antibody (ANA) (>95%); anti-dsDNA (40– 60%); anti-Sm (20–30%); antihistone antibodies; nonhistone nuclear RNA proteins; and blood cells.

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SLE affects **many organ systems**

- Hematologic (type II hypersensitivity reaction) manifestations can include hemolytic anemia, thrombocytopenia, neutropenia, and lymphopenia.
- Skeletal manifestations include arthritis characterized by polyarthralgia and synovitis without joint deformity (type III hypersensitivity reaction).
- Skin (type III hypersensitivity reaction) manifestations can include a malar “butterfly” rash; maculopapular rash; and ulcerations and bullae formation.
- Serosal surfaces may also be affected, with resulting pericarditis, pleuritis, or pleural effusions (type III hypersensitivity reaction).
- Central nervous system manifestations include focal neurologic symptoms, seizures, and psychosis (type III hypersensitivity reaction).
- Cardiac manifestations include Libman-Sacks endocarditis (nonbacterial verrucous endocarditis) (type III hypersensitivity reaction).

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Of importance are the renal manifestations (type III hypersensitivity) classified by the Society of Nephrology/Renal Pathology Society as follows.

- Class I: minimal mesangial lupus nephritis
- Class II: mesangial proliferative lupus nephritis
- Class III: focal (< 50%) lupus nephritis
- Class IV: diffuse (> 50%) lupus nephritis
- Class V: membranous lupus nephritis
- Class VI: advanced sclerosing lupus nephritis

Lupus is treated with steroids and immunosuppressive agents. It tends to have a chronic, unpredictable course with remissions and relapses. The 10-year survival is 85%, with death frequently being due to renal failure or infections.

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Sjögren syndrome (sicca syndrome) is an autoimmune disease characterized by destruction of the lacrimal and salivary glands, resulting in the inability to produce saliva and tears. Females are affected more often than males, with typical age 30–50.

Clinical manifestations include

- keratoconjunctivitis sicca (dry eyes) and corneal ulcers;
- xerostomia (dry mouth); and Mikulicz syndrome (enlargement of the salivary and lacrimal glands).
- Sjögren syndrome is often associated with rheumatoid arthritis and other autoimmune diseases.

Lab finding: The characteristic autoantibodies are the anti-ribonucleoprotein antibodies SS-A (Ro) and SS-B (La).

Prognosis: There is an increased risk of developing non-Hodgkin lymphoma.

Immunopathology

Scleroderma (progressive systemic sclerosis) is an autoimmune disease characterized by fibroblast stimulation and deposition of collagen in the skin and internal organs. It affects females more than males, with typical age range of 20 to 55 years. The pathogenesis involves activation of fibroblasts by cytokines interleukin 1 (IL-1), platelet-derived growth factor (PDGF), and/or fibroblast growth factor (FGF) with the resulting activated fibroblasts causing fibrosis.

Diffuse scleroderma has anti-DNA topoisomerase I antibodies (Scl-70) (70%), widespread skin involvement, and early involvement of the visceral organs. Organs that can be affected include the oesophagus (dysphagia), GI tract (malabsorption), lungs (pulmonary fibrosis which causes dyspnoea on exertion), heart (cardiac fibrosis which may manifest as arrhythmias), and kidney (fibrosis that may manifest as renal insufficiency).

Immunopathology

Localized scleroderma (CREST syndrome) has anti-centromere antibodies, skin involvement of the face and hands, late involvement of visceral organs, and a relatively benign clinical course.

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Dermatomyositis and polymyositis. See Skeletal Muscle chapter.

Mixed connective tissue disease is an overlap condition with features of systemic lupus erythematosus, systemic sclerosis, and polymyositis. Antiribonucleoprotein antibodies are nearly always positive.

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PRIMARY IMMUNE DEFICIENCY SYNDROMES

B cell Defect

X linked a gammaglobulinemia Bruton

CVID

Immunopathology

X-linked agammaglobulinemia of Bruton is an immunodeficiency characterized by a developmental failure to produce mature B cells and plasma cells, resulting in agammaglobulinemia. The condition occurs because of loss of function mutations of B-cell Bruton tyrosine kinase (BTK). Clinically, the disease affects male infants who have recurrent infections beginning at 6 months of life due to the loss of passive maternal immunity. Common infections include pharyngitis, otitis media, bronchitis, and pneumonia; common infecting organisms include

H. influenza, S. pneumococcus, and *S. aureus*.

Immunopathology

Common variable immunodeficiency is a group of disorders characterized by defects in B-cell maturation that can lead to defective IgA or IgG production.

Clinically, both sexes are affected with onset in childhood of recurrent bacterial infections and with increased susceptibility to *Giardia lamblia*. Complications include increased frequency of developing autoimmune disease, non-Hodgkin lymphoma, and gastric cancer.

Immunopathology

DiGeorge syndrome is an embryologic failure to develop the 3rd and 4th pharyngeal pouches, resulting in the absence of the parathyroid glands and thymus.

Clinical findings can include neonatal hypocalcaemia and tetany, T-cell deficiency, and recurrent infections with viral and fungal organisms.

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Severe combined immunodeficiency (SCID)

It is a combined deficiency of cell-mediated and humoral immunity that is often caused by a progenitor-cell defect.

The modes of inheritance are variable and can include X-linked (mutation of the common [gamma] chain of the interleukin receptors IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21) and autosomal recessive (deficiency of adenosine deaminase).

Clinical features include recurrent infections with bacteria, fungi, viruses, and protozoa; susceptibility to *Candida*, cytomegalovirus (CMV) and *Pneumocystis Jeroveci* infections, and adverse reactions to live virus immunizations. SCID is treated with hematopoietic stem cell transplantation since the prognosis without treatment is death of most infants within a year.

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Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome is an X-linked recessive disease with mutation in the gene for Wiskott-Aldrich syndrome protein (WASP).

The disease has a clinical triad of recurrent infections, severe thrombocytopenia, and eczema (chronic spongiform dermatitis). Treatment is hematopoietic stem cell transplantation.

Complications include increased risk of non-Hodgkin lymphoma and death due to infection or hemorrhage

Immunopathology

Complement system disorders can involve a variety of factors, with deficiencies of different factors producing different clinical patterns. In both the classical and alternate pathways, C3 deficiency causes both recurrent bacterial infections and immune complex disease, while C5, C6, C7, and C8 deficiencies cause recurrent meningococcal and gonococcal infections.

- In the classical pathway only, C1q, C1r, C1s, C2, and C4 deficiencies cause marked increases in immune complex diseases, including infections with pyogenic bacteria.
- In the alternate pathway, Factor B and properdin deficiencies cause increased neisserial infections. Deficiencies in complement regulatory proteins can cause C1-INH deficiency (hereditary angioedema), which is characterized clinically by edema at mucosal surfaces with low C2 and C4 levels.

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MHC class II deficiency can be caused by defects in positive selection of thymocytes. Few CD4+ lymphocytes develop and as a result, patients suffer from severe immunodeficiency. Mutations in genes (i.e., CIITA) that encode proteins that regulate MHC class II gene expression are the cause. CD8+ T cells are unaffected.

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Hyper IgM syndrome

Hyper IgM syndrome is characterized by normal B and T lymphocyte numbers and normal to elevated IgM levels but significantly decreased IgA, IgG and IgE levels. Mutations in the gene for CD40 ligand result in the most common form of X-linked hyper IgM syndrome.

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Selective IgA deficiency

Selective IgA deficiency has unknown genetic Etiology. Many affected individuals appear healthy while others have significant illness. Sinopulmonary infections, diarrhoea and adverse reactions to transfusions can occur. Levels of IgA are undetectable whereas levels of other isotypes are normal. There is an association with autoimmune disease.

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Phagocyte deficiencies (See chronic granulomatous disease in Inflammation chapter.)

LAD

CGD

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SECONDARY IMMUNE DEFICIENCY SYNDROMES

Systemic diseases that can cause secondary immunodeficiency include diabetes mellitus, collagen vascular disease (e.g., systemic lupus erythematosus), and chronic alcoholism. Secondary immunodeficiency is more common.

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ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

AIDS can be diagnosed when a person is HIV-positive and has CD4 count <200 cells/mL, or when a person is HIV-positive and has an AIDS-defining disease. Males are affected more frequently than females.

The human immunodeficiency virus (HIV) is an enveloped RNA retrovirus that contains reverse transcriptase. HIV infects CD4-positive cells, includingCD4+ T lymphocytes, all macrophages, lymph node follicular dendritic cells, and Langerhans cells. The mechanism of infection is by binding of CD4 by the viral gp120, followed by entry into cell by fusion, which requires gp41 and coreceptors CCR5 (β-chemokine receptor 5) and CXCR4 (α-chemokine receptor).

Immunopathology

Transmission of HIV can occur by many mechanisms, including sexual contact (most common mode, including both homosexual transmission and an increasing rate of heterosexual transmission, with important cofactors including herpes and syphilis infection); parenteral transmission; IV drug use; blood transfusions (including those done in haemophiliacs); accidental needle sticks in hospital workers; and vertical transmission.

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Diagnosis. The CDC recommends initial testing with an antigen/antibody combination immunoassay, followed by a confirmatory HIV-1/HIV-2 antibody differentiation immunoassay. If the confirmatory test is negative, testing with an HIV-1 nucleic acid test is done. Treatment varies, and can include combination antiretroviral treatment, reverse transcriptase inhibitors, protease inhibitors, and prophylaxis for opportunistic infections based on CD4 count.

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The clinical manifestations of HIV infection vary over time. The acute phase is characterized by viremia with a reduction in CD4 count, mononucleosis-like viral symptoms and lymphadenopathy, and seroconversion.

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The latent phase is characterized by asymptomatic or persistent generalized lymphadenopathy with continued viral replication in the lymph node and spleen, low level of virus in the blood, and minor opportunistic infection including oral thrush (candidiasis) and herpes zoster. The average duration of latent phase is 10 years.

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Progression to AIDS (third phase) occurs with reduction of CD4 count to <200 cells/mL, which is accompanied by re-emergence of viremia and development of AIDS-defining diseases, possibly to eventual death.

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Opportunistic Infection and Common Sites of Infection in AIDS Patients

Opportunistic Infection	Common Sites of Infection
Pneumocystis Jeroveci	Lung (pneumonia), bone marrow
Mycobacterium tuberculosis	Lung, disseminated
Mycobacterium avium-intracellular.	Lung, GI tract, disseminated
Coccidioidomycosis	Lung, disseminated
Histoplasmosis	Lung, disseminated
Cytomegalovirus	Lung, retina, adrenals, and GI tract
Giardia lamblia	GI tract
Cryptosporidium	GI tract

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Herpes simplex virus Esophagus and CNS (encephalitis)

Candida Oral pharynx and esophagus

Aspergillus CNS, lungs, blood vessels

Toxoplasmosis CNS

Cryptococcus CNS (meningitis)

JC virus CNS (progressive multifocal leukoencephalopathy)

Bartonella spp. Skin, mucosa, bone (bacillary angiomatosis)

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AIDS-Defining Diseases

Hairy leukoplakia is an Epstein-Barr virus (EBV)–associated condition due to infection of squamous cells. White plaques are present on the tongue. Kaposi sarcoma is the most common neoplasm in AIDS patients. (See Vascular Pathology chapter.)

Non-Hodgkin lymphomas tend to be high-grade B-cell lymphomas; extra nodal CNS lymphomas are common. Other AIDS-defining diseases include cervical cancer, HIV-wasting syndrome, AIDS nephropathy, and AIDS dementia complex.

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IMMUNOLOGY OF TRANSPLANT REJECTION

Rejection is caused largely by differences in HLA alleles between donor and recipient. Immunosuppressive agents are used to prevent and mitigate rejection.

- Hyperacute rejection occurs within minutes to hours due to preformed antibodies in the recipient. Lymphocyte cross-matching has almost eliminated this problem.
- Acute rejection occurs in the first 6 months and may be cellular (CD8+ T lymphocytes kill graft cells) or antibody-mediated.
- Chronic rejection occurs after months or years and may be cell-mediate or antibody-mediated. The vasculature components are targeted, and the histopathologic changes depend on the organ involved.

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