8+9) Hypersensitivity

Part 1: Hypersensitivity Overview and Type I & II

Introduction and Classification

- Hypersensitivity refers to immune responses that cause tissue injury due to being **excessive or aberrantly directed**.
- It is caused by responses to **foreign antigens** (repetitive or poorly controlled) or **self-antigens** (autoimmunity).
- Classification is based on the **immune mechanism**, not timing.

Type I: Immediate Allergic Reactions

- **Mechanism**: Caused by **IgE antibodies** against environmental antigens (atopy/allergy).
- **Sensitization**: Initial exposure leads to IgE production and binding to **FcεRI** receptors on mast cells.
- **Activation**: Re-exposure cross-links IgE, causing **mast cell degranulation**.
- **Mediators**:
    - **Histamine**: Vasoactive amine causing vasodilation and smooth muscle contraction.
    - **Leukotrienes (C4, D4, E4)**: Prolonged bronchoconstriction and mucus.
    - **Cytokines (IL-4, IL-5, IL-13)**: Critical for IgE class-switching and **eosinophil recruitment**.
- **Phases**:
    - **Immediate (5-30 min)**: Edema, redness, and pruritus.
    - **Late-phase (2-24 h)**: Driven by **eosinophils** and Th2 cells; causes epithelial injury.
- **Specific Outcomes**: **Allergic Rhinitis** (hay fever), **Allergic Asthma** (airway remodeling and muscle hypertrophy), **Atopic Dermatitis** (eczema/atopic march), and **Systemic Anaphylaxis** (vascular collapse/shock).
- **Treatment**: Antihistamines, corticosteroids, epinephrine (for anaphylaxis), and monoclonal antibodies blocking IgE or Th2 cytokines.

Type II: Antibody-Mediated Diseases

- **Mechanism**: Mediated by **IgG or IgM** binding to **cell or tissue antigens**.
- **Injury Mechanisms**:
    - **Opsonization and Phagocytosis**: Cells (like RBCs) are cleared in the spleen/liver.
    - **Complement/Fc Receptor Inflammation**: Recruits neutrophils that release enzymes/ROS.
    - **Receptor Dysfunction**: Antibodies stimulate or block receptors (Graves' or Myasthenia Gravis).
- **Examples**: **Autoimmune Hemolytic Anemia**, **Goodpasture Syndrome** (necrotizing inflammation in lungs/kidneys), and **Rheumatic Fever**.

Part 2: Type III & IV and Specific Autoimmune Diseases

Type III: Immune Complex-Mediated Diseases

- **Mechanism**: **Antigen-antibody complexes** (typically **IgG**) deposit in blood vessels.
- **Pathogenesis**: Occurs when complexes are formed in **excessive amounts** or there is **inefficient removal**.
- **Deposition**: **Positively charged antigens** are particularly pathogenic as they bind negatively charged basement membranes.
- **Sites**: Usually systemic; common in **renal glomeruli** and **joint synovium**.
- **Injury**: Complexes activate **complement** and bind **Fc receptors on neutrophils**, causing **vasculitis** (vessel wall inflammation), local hemorrhage, and thrombosis.
- **Examples**: **Systemic Lupus Erythematosus (SLE)**, **Polyarteritis Nodosa**, and **Serum Sickness**.
- **Arthus Reaction**: A localized experimental vasculitis induced by subcutaneous injection.

Type IV: T Lymphocyte-Mediated Diseases

- **Mechanism**: Tissue injury results from **T-cell mediated inflammation** or **cytotoxicity**.
- **CD4+ T Cells**: Induce inflammation via cytokines (**Th1** produces IFN-\gamma; **Th17** recruits neutrophils).
- **CD8+ CTLs**: Direct killing of host cells.
- **Delayed-Type Hypersensitivity (DTH)**: Occurs **24-48 hours** after antigen challenge (e.g., **PPD skin test** for TB).
- **Examples**: **Type 1 Diabetes**, **Multiple Sclerosis (MS)**, and **Rheumatoid Arthritis (RA)**.

Specific Multisystem/Organ Diseases

- **SLE**: Chronic multisystem disease; **female to male ratio 10:1**. Characterized by **antinuclear antibodies (ANA)**, specifically against **dsDNA**. Pathogenesis involves **HLA DR2/DR3**, **complement deficiency (C1q, C2, C4)**, and **UV light**.
- **Rheumatoid Arthritis**: Chronic synovial inflammation destroying cartilage/bone. Driven by **Th1 and Th17 cells**. Diagnostic markers include **Rheumatoid factor** and **Anti-CCP**. Associated with **HLA DR4**.
- **Type 1 Diabetes**: Destruction of **insulin-producing beta cells**; characterized by **insulitis** (lymphocytic infiltration). Associated with **HLA DR3, DR4, DQ2, and DQ8**.
- **Multiple Sclerosis**: Demyelination of CNS white matter by **Th1 and Th17** cells. Associated with **HLA DR2**.

Summary Table

Type	Principal Immune Mechanism	Key Mediators	Clinicopathologic Manifestations	Typical Examples
I (Immediate)	**IgE**, Mast cells, Th2 cells	**Histamine**, Leukotrienes, Th2 cytokines	Edema, bronchoconstriction, mucus, pruritus	Anaphylaxis, Asthma, Hay fever, Eczema
II (Antibody)	**IgG/IgM** against cell/matrix antigens	Complement, **Fc receptors**, Phagocytes	Opsonization/Phagocytosis, Inflammation, Receptor dysfunction	Hemolytic anemia, Graves', Myasthenia Gravis
III (Complex)	**Immune complexes** in vessels	**Complement**, **Neutrophils** (Proteases/ROS)	**Vasculitis**, Glomerulonephritis, Arthritis	SLE, Serum Sickness, Arthus Reaction
IV (T-cell)	**CD4+** (inflammation) & **CD8+** (killing)	**Cytokines** (IFN-\gamma, IL-17), Macrophages	**DTH reaction**, Granulomas, Islet/Myelin destruction	MS, Type 1 Diabetes, RA, Contact sensitivity