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Classification of Immune Mediated Tissue Injury

Tuesday, February 19, 2008
10:00 AM

- Type I: Anaphylactic Type
  - Allergen binding to mass cell to cause degranulation
  - Prototype disorders
    - Allergic rhinitis
    - Asthma
    - Anaphylaxis (insect venom)
  - Immune mechanism
    - IgE-Mast cell binding
    - Vascular permeability
    - Eosinophils
  - Clinical
    - Result of exposure to environmental allergens in genetically susceptible individuals
    - Genetics not clearly defined, but association exists
    - Atopy: genetic predisposition for developing IgE responses to many antigens
    - Local or systemic symptoms
    - Most common form - allergic rhinitis
      - Certain types of asthma
      - Atopic dermatitis (eczema)
      - GI food allergies
    - Allergens: pollens, molds, house dust mites, animal dander
  - Pathophysiology
    - Antigen presented by APC to Th cell --> IL-4 activation of B cell
    - IgE antibodies secreted by B cell
    - IgE antibodies bind to Fc receptors on mast cells
    - Antigen binds to IgE on mast cells
    - Degranulation of mast cell releases cytokines
      - IL-4,5,6 stimulates B cells
      - IL-3,4 stimulates GM-CSF, TNF-α, IL-8/0, inflammatory cell activation
    - Mediators have variety of effects
      - Increase vascular permeability
      - Constrict airways
      - Cell infiltration
      - Asthma, eczema, hay fever
      - Feedback effects on immune system
  - Effects of mediators
    - Histamine --> vascular permeability, vasodilation of post-capillary venule, smooth muscle contraction
    - Chemotactic factors
    - Cytokines
    - Lipid mediators
      - Arachidonic acid metabolites: LTC4,D4,E4 --> smooth muscle contraction; prostaglandins --> vasodilation
      - PAF - platelet activating factor
      - Acetylated glycerol ether phosphocholine --> activates phagocytic cells, smooth muscle contraction
  - Eosinophils
    - Normal levels: 2 to 3% of total WBCs
    - Type 1 response: up to 10%
- Secretory products
  - NADPH oxidase derived oxidants
  - Prostaglandins and leukotrienes (LTC4)
  - Major basic protein: cytotoxic
  - Cytokines
  - Others
- Symptoms depends on tgt organ
  - Skin
    - Gross: swelling, wheal and flare
      - Early: preformed mediators
      - Late: synthesized mediators
    - LM: edema, eosinophils
    - EM: edema, endothelial cell gaps
  - Mucous and serous glands: increased secretion
  - Bronchial and GI smooth muscle contraction
- Therapeutics
  - Avoid antigen
  - Mediator antagonists
    - Anti-histamines: receptor antagonist
    - Leukotriene inhibitors: lipase inhibitors, receptor antagonists
    - Fxnl: sympathetic stimulatants (EPI)
  - Inhibit mast cell degranulation: cromolyn
  - Non-specific anti-inflammatory agents: corticosteroids
  - Immunotherapy: "allergy shots"
- Diagnosis
  - Skin tests: swell, wheal, flare (w/in mins) --> Type I hypersensitivity
  - RAST: bead w/ Ag + pt’s serum + antihuman IgE --> if fluorescent --> allergic
  - RIST: bead + anti-human IgE + serum --> how much IgE
- Type II, Cytotoxic type
  - Involves binding of IgG to tgt cell and cytotoxic action/complement activation
  - Prototype disorders
    - Hemolytic rxns
    - Goodpastures syndrome
    - Myasthenia gravis
    - Grave's disease (hyperthyroidism)
  - Immune Mechanisms
    - IgG
    - Complement
    - Phagocytic cells
    - ADCC
  - Pathophysiology
    - Binding of antibody w/ cell membrane or tissue antigens
    - RBC membrane antigens - hemolytic anemias
      - Mother is Rh-
      - First baby is Rh+
      - Mother develops anti-Rh+ IgG
      - 2nd child is Rh+
      - IgG crosses placenta
      - Binds to RBC of fetus --> hemolysis
      - Treat by blocking sensitization of mother anti-D Ig w/in 72 hrs of first birth
    - Platelet antigens - thrombocytopenia cell membrane - petechiae
    - Basement membrane - goodpasture's syndrome (kidney, lung)
  - Mechanisms
    - Opsonin dependent phagocytosis
• Complement dependent Ab lysis
• Ab-dependent cell cytotoxicity
• Examples
  □ Goodpasture's: antigen is basement membrane of kidney and lung
  □ Dermatitis herpetiformis: basement membrane reticulin
  □ Bullous pemphigoid: epidermis basement membrane
  □ Pemphigus vulgaris: epidermis keratinocyte membrane
• N'phil, frustrated phagocytosis, extracellular enzyme release
  ○ Goodpasture's
    ▪ Hemoptysis, pulmonary infiltrates, renal failure, anemia
• Pathology
  □ Circulating anti-GBM antibodies
  □ LM: n'phils, hemorrhage
  □ Immunofluoresence: Ig and complement deposition; linear
    ◆ Linear antigen deposition --> Ab + complement deposition --> linear secondary anti-human Ab to IgG or complement contain fluorescent marker
  □ EM: no electron dense deposits
• Antibody binds to GBM --> complement --> C3b deposition + C3a/C5a --> PMN recruitment --> proteases + ROS --> tissue injury
• Lung: hemorrhage, hemoptysis, alveolar infiltrates
• Kidney: proteinuria, hematuria, renal failure
  ○ Antibody binding to cell receptor (Type V rxns)
    ▪ Grave's disease: IgG binds to TSH-R and stimulates cell to make T3/T4
    ▪ Myasthenia Gravis: Ab to Ach-R at synapse blocks neuromuscular transmission --> muscle weakness
• Type III, Immune Complex Disease
  ○ Antibody binds to antigen and deposits on tissues
  ○ Protoype disorders
    ▪ Post-strep glomerulonephritis
    ▪ Vasculitis: polyarteritis nodosa
  ○ Immune mechanisms
    ▪ Ab-Ag rxns
    ▪ Complement
    ▪ Neutrophils
    ▪ Fibrin, hemorrhage
  ○ Pathophysiology
    ▪ Ag-Ab complex deposits in tissues
    ▪ Complement activation via IgG/IgM --> C5a
    ▪ Monocyte/mphage activation --> cytokines
    ▪ N'phil influx
    ▪ Phagocytosis of immune complexes
    ▪ Release of ROS and lysosomal enzymes
    ▪ Tissue Injury (fibrinoid necrosis, hemorrhage, n'phils, Ab+complement deposition
    ▪ LM: n'phils, hemorrhage, edema
    ▪ EM: electron dense deposits
    ▪ Granular immunofluorescene
  ○ Systemic Immune Complex Disease
    ▪ Foreign antigen injected IV
    ▪ Immune response w/ Ab prod (IgM, IgG)
    ▪ Circulating immune complexes formed
    ▪ Tissue deposition w/ complement fixation
    ▪ Arteritis/glomerulonephritis (w/ proteinuria)
  ○ Clinical
    ▪ Depends on tgt organ and/or site of immune complex deposition
- Synovium - RA
- Kidney - glomerulus
  - Post-strep glomerulonephritis --> granular immunofluorescence
  - Systemic lupus erythematosus
- Blood vessel walls - vasculitis
  - Polyarteritis nodosa
  - Early transplant rejection
- Lung - hypersensitivity pneumonitis
  - Diagnosis
    - Skin tests for Type III rxns
    - Takes several hours to manifest b/c requires complement fixation
  - Treatment
    - Elimination of antigen - tranfusion rxns, hypersensitivity lung rxns to foreign antigens, certain drug rxns
    - Corticosteroid and immunosuppressive therapy (cytoxan, cyclosporin, anti-TNFs)
    - Plasmapheresis - filtration of plasma antibodies
- Type IV, Cell-Mediated (Delayed) Hypersensitivity
  - Antigen binding to T cells causes m'phage activation and release of inflammatory mediators
  - Prototype Disorders
    - Poison Ivy, epidermal
      - Eczema
      - Infiltration of lymphocytes and later macrophages, edema
      - 1st contact sensitizes --> creation of T memory cells
      - 2nd contact --> T memory cells --> Th cells --> mphase activation --> dermatitis
    - Tuberculosis
      - Local hardening and swelling +/- fever
      - Infiltration of lymphocytes, monocytes and mphages
      - Intradermal injection used diagnostically, tuberculin, mycobacterial and leishmainial antigens
    - Granulomatous
      - 4 wk rxn time
      - Hardening in skin or lung
      - Granuloma containing epithelioid cells, giant cells, mphpages; fibrosis +/- necrosis
      - Persistent Ag or Ag-Ab complexes in mphpages or non-immunological
    - Cytotoxic T-Cells
      - Immune Mechanisms
        - T-lymphocytes
        - Monocytes/macrophages
      - Sensitization phase
        - Hapten enters and is taken up by Langerhans' cells in skin
        - Migrates to lymph node
        - Germinal center forms --> T cells proliferate
      - Contact hypersensitivity
        - Hapten enters and is carried to circulation
        - Binds to langerhans cel
        - CD8, Th1 cells activated
        - Macrophage activated
      - Granulomatous Inflammatory Rxns
        - APC-Th1 interaction --> IL-2 --> T cell proliferation
        - IL-3,6, IFN-y, TNF --> mphase activation --> epithelioid cell --> TNF causes fusion to make giant cell
        - Mphpages and lymphocytes surround antigen-antibody complexes to prevent spread
      - Skin Test takes 48-72 hours
- T-Cell Mediated Cytotoxicity
○ Mechanisms
  ▪ CD8+ T cell
  ▪ Antigen expressed w/ class I MHC
  ▪ IL-2 clonal expansion
  ▪ Cytotoxic effector cell recognizes Ag+class I MHC
○ Initiates programmed cell death
  ▪ Perforins/cytolysins
  ▪ Proteolytic enzymes: granzymes
  ▪ FAS-induced apoptosis: CD8+ T cell:FAS ligand
  ▪ Cytokines: IFNγ, TNFα/β