Immune Diseases  Kristine Krafts, M.D.
Immune Diseases Outline

Autoimmune diseases
  • Immunologic tolerance and autoimmunity
  • Specific diseases

Primary immune deficiencies
  • Basic concepts
  • Specific diseases
Autoimmune diseases
  • Immunologic tolerance and autoimmunity
“Tolerance” = unresponsiveness to an antigen
“Self-tolerance” = unresponsiveness to one’s own antigens
In generating billions of B and T cells, some will react against self antigens!
There are two ways of muzzling these cells: central tolerance and peripheral tolerance
Immunologic Tolerance

Central tolerance
- Auto-reactive T and B cells deleted during maturation
- Occurs by apoptosis in thymus and bone marrow
- Process not perfect (some get out!)

Peripheral tolerance
- Auto-reactive cells muzzled in peripheral tissues
- Some become “anergic” (inactive) in periphery
- Some are suppressed by regulatory T cells
- Some undergo apoptosis when activated
Autoimmunity

- “Autoimmunity” = immune reaction against self
- Self-tolerance breaks down, causing disease
- Two main reasons for breakdown:
  - Genes
    - HLA-DR4: ↑ risk of rheumatoid arthritis
    - HLA-B27: ↑ risk of ankylosing spondylitis
  - Environmental triggers
    - Expose hidden self-antigens
    - Activate APCs
    - Mimic self antigens
Genetic susceptibility

Infection, tissue damage

Susceptibility genes

Infections, inflammation

Failure of self-tolerance

Activation of tissue APCs

Self-reactive lymphocytes

Influx of self-reactive lymphocytes into tissues

Activation of self-reactive lymphocytes

Tissue injury: autoimmune disease
Autoimmune diseases
  • Immunologic tolerance and autoimmunity
  • Specific diseases
Immune Diseases Outline

Autoimmune diseases
• Immunologic tolerance and autoimmunity
• Specific diseases
  • Lupus
Lupus

Things You Must Know

- Typical patient: young woman with butterfly rash
- Symptoms unpredictable (relapsing/remitting)
- Multisystem (skin, kidneys, joints, heart)
- Antinuclear antibodies
Autoantibodies!

- Antinuclear Ab present in all patients with SLE... but found in other autoimmune diseases too
- Anti-RBC, -lymphocyte, -platelet, or –phospholipid antibodies may be present too

Underlying cause unclear

- Genetic predisposition...
- ...plus triggers (UV radiation, drugs)
What’s so bad about having these autoantibodies?

They cause tissue injury!

- Form immune complexes
- Cause destruction, phagocytosis of cells

Multisystem effects:

- Kidney (renal failure)
- Skin ("butterfly rash")
- CNS (focal neurologic deficits)
- Joints (arthritis)
- Heart (pericarditis, endocarditis)
Discoid Lupus

- Skin involvement only
- May evolve into systemic lupus
EM of glomerular capillary loop: subendothelial deposits
Glomerulus: “wire loop” appearance
Heart valve: Libman-Sacks lesions
Heart valve: Libman-Sacks lesions
Lupus: Things a Dentist Might See

- Young woman with polyarthritis and a butterfly (or other) skin rash
- Fatigue
- Sensitivity to sunlight
- Headaches, seizures, or psychiatric problems
- Pleuritic chest pain
- Unexplained fever
- Oral lesions (rare): nonspecific, red-white, erosive
Lupus: butterfly rash
Lupus: butterfly rash
Lupus facial lesions
Lupus: vasculitic rash
Lupus: “hitch-hiking thumb”
Lupus mucosal lesions
Lupus palatal lesions
Lupus Prognosis

- Variable! Some have few symptoms, rare patients die within months.
- Most patients: relapses/remissions over many years.
- Acute flare-ups controlled with steroids
- 80% 10-year survival
- Most common cause of death: renal failure
Autoimmune diseases

• Immunologic tolerance and autoimmunity
• Specific diseases
  • Lupus
  • Rheumatoid arthritis
Rheumatoid Arthritis

Things You Must Know

- Symmetric, mostly small-joint arthritis
- Systemic symptoms (skin, heart, vessels, lungs)
- Rheumatoid factor
- Cytokines (especially TNF) cause damage
RA Etiology

- Genetically predisposed patient
- Something (bug? self-Ag?) activates T cells
- T cells release cytokines:
  - activate macrophages (causing destruction)
  - cause B cells to make antibodies against joint
  - Most important of these cytokines: TNF
- Cytokines cause inflammation and tissue damage
• Mainly small joints (hands), but also knees, elbows, shoulders
• Symmetric; characteristic hand features
• Chronic synovitis with pannus formation:
  • synovial cell proliferation
  • inflammation
  • granulation tissue
Rheumatoid arthritis joint lesion
Rheumatoid arthritis: villi (L) and lymphoid aggregates (R)
Rheumatoid arthritis joint deformities

- Boutonniere deformity of thumb
- Ulnar deviation of metacarpophalangeal joints
- Swan-neck deformity of fingers

Rheumatoid arthritis (late stage)
RA Systemic Disease

- Weakness, malaise, fever
- Vasculitis
- Pleuritis, pericarditis
- Lung fibrosis
- Eye changes
- Rheumatoid nodules on forearms
Rheumatoid nodules
Rheumatoid Factor

- Circulating IgM antibody
- Directed against patient’s OWN IgG!
- Forms IgM-IgG immune complexes, which deposit in joints and cause badness
- Present in 80% of patients
RA: Things a Dentist Might See

- Female patient with aching, stiff joints, especially in morning
- Symmetric joint swelling
- Fingers: ulnar deviation, swan-neck deformities, boutonniere deformities
- Rheumatoid nodules
Rheumatoid arthritis joint deformities
RA: Prognosis

- Variable!
- A few patients stabilize
- Most patients have chronic course with progressive joint destruction and disability
- Lifespan shortened by 10-15 years
- Treatment: steroids, anti-TNF agents
Immune Diseases Outline

Autoimmune diseases

• Immunologic tolerance and autoimmunity
• Specific diseases
  • Lupus
  • Rheumatoid arthritis
  • Sjögren syndrome
Sjögren Syndrome

Things You Must Know

- Inflammatory disease of salivary and lacrimal glands
- Dry eyes, dry mouth
- T cells react against some Ag (self? viral?) in gland; gland gets destroyed
- Increased risk of lymphoma
• CD4+ T cells attack self antigens in glands (why?!)
• Autoantibodies are present, but probably are not the primary cause of tissue injury
  • ANAs
  • RF
  • Anti-SS-A, anti-SS-B
• Viral trigger?
• Genetic predisposition
Sjögren Signs and Symptoms

Salivary and lacrimal glands
• enlarged
• marked inflammation and gland destruction
• 40x increased risk of lymphoma!

Systemic disease
• fatigue
• arthralgia/myalgia
• Raynaud phenomenon
• vasculitis
• peripheral neuropathy
• often, patient has another autoimmune disease too
Sjögren: Things a Dentist Might See

- Female between 35-45
- Enlarged salivary glands
- Raynaud phenomenon
- Keratoconjunctivitis sicca (dry eyes)
- Oral changes:
  - xerostomia (dry mouth)
  - mucosal atrophy
  - candidiasis
  - mucosal ulceration
  - dental caries
  - taste dysfunction
Sjögren syndrome: salivary gland enlargement
oral changes in sjögren syndrome

atrophic papillae, deeply fissured epithelium

angular cheilitis

missing teeth and multiple caries
Sjögren Treatment

- Treatment is mostly supportive and symptom-based
- Oral treatment: adequate hydration, scrupulous dental hygiene, cholinergic agents (stimulate saliva release), frequent dental exams
- Eye treatment: lubricating solutions, surgical procedures
- Systemic symptom treatment: steroids, other immunosuppressive drugs
Immune Diseases Outline

Autoimmune diseases
  • Immunologic tolerance and autoimmunity
  • Specific diseases
    • Lupus
    • Rheumatoid arthritis
    • Sjögren syndrome
    • Scleroderma
Scleroderma (Systemic Sclerosis)

Things You Must Know

- Excessive fibrosis throughout body: skin, viscera
- Claw hands, mask-like face
- Microvascular disease also present
- Diffuse and limited types
Scleroderma Etiology

- CD4+ T cells accumulate for some reason
- T cells release cytokines that activate mast cells and macrophages, which release fibrogenic cytokines
- B cell activation also occurs (diagnostic antibody: anti-Scl 70) but doesn’t play major role
- The cause of microvascular changes is unknown
Scleroderma Signs and Symptoms

- Skin: diffuse, sclerotic atrophy. Fingers first.
- GI: “rubber-hose” lower esophagus
- Lungs: fibrosis, pulmonary hypertension
- Kidneys: narrowed vessels, hypertension
- Heart: myocardial fibrosis
Scleroderma: claw hands
Scleroderma: sclerotic skin
Scleroderma: fibrosis in alveolar walls
Scleroderma: narrowed renal vessel
Scleroderma: Limited Type

- Mild skin involvement (face, fingers)
- Involvement of viscera occurs later
- Also called CREST syndrome
  - Calcinosis
  - Raynaud phenomenon
  - Esophageal dysmotility
  - Sclerodactyly
  - Telangiectasia
- Benign course
Scleroderma: calcinosis
Scleroderma: calcinosis
Scleroderma: Raynaud phenomenon
Scleroderma: sclerodactyly
Scleroderma: telangiectasias
Scleroderma: telangiectasias
Scleroderma: Diffuse Type

- Initial widespread skin involvement
- Early visceral involvement
- Rapid course
Scleroderma: Things a Dentist Might See

- Female between 50-60
- Raynaud phenomenon
- Stiff, clawlike fingers
- Mask-like face
- Difficulty swallowing
- Dyspnea, chronic cough
- Difficulty getting dentures in
Scleroderma: restricted mouth opening
Scleroderma Prognosis

- Steady, slow, downhill course over years
- Limited scleroderma may exist for decades without progressing
- Diffuse scleroderma is more common and has worse prognosis
- Overall 10-year survival = 35-70%
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  • Basic concepts
Basic Concepts

- Immune deficiencies
  - primary (inherited)
  - secondary (to infection, immunosuppression, etc.)
- Patients more susceptible to infections and cancer
- Type of infection varies:
  - Ig, C’ or phagocytic cell defect: bacterial infection
  - T cell defect: viral and fungal infections
- This lecture covers primary immune deficiencies
Primary Immune Deficiencies

• Rare!
• Genetic
• Can affect any part of immune system:
  • Adaptive (humoral or cellular)
  • Innate (C’, phagocytes, NK cells)
• Typical patient: infant with recurrent infections
• Primary importance for our class: boards
X-linked agammaglobulinemia

SCID

DiGeorge syndrome

Hyper-IgM syndrome

CVID

IgA deficiency
Immune Diseases Outline

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    • X-linked agammaglobulinemia
X-Linked Agammaglobulinemia

- Pre-B cells can’t differentiate into B cells
- Patients have no immunoglobulin
- Affects males
- Presents at 6 months of age (maternal Ig gone)
- Recurrent bacterial infections
- Treatment: intravenous pooled human Ig
Immune Diseases Outline

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Primary immune deficiencies
  • Basic concepts
  • Specific diseases
    • X-linked agammaglobulinemia
    • Common variable immunodeficiency
Common Variable Immunodeficiency

- Group of disorders characterized by defective antibody production
- Affects males and females equally
- Presents in teens or twenties
- Basis of Ig deficiency is variable (hence the name) and often unknown
- Patients more susceptible to infections, but also to autoimmune disorders and lymphoma!
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    • Common variable immunodeficiency
    • Isolated IgA deficiency
Isolated IgA Deficiency

- Most common of all primary immune deficiencies
- Cause is unknown
- Most patients asymptomatic
- Some patients get recurrent sinus/lung infections or diarrhea (IgA is the major Ig in mucosal secretions)
- Possible anaphylaxis following blood transfusion (patients have anti-IgA antibodies, and there is IgA in transfused blood!)
- Increased incidence of autoimmune disease (who knows why)
Immune Diseases Outline

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Primary immune deficiencies
- Basic concepts
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  - X-linked agammaglobulinemia
  - Common variable immunodeficiency
  - Isolated IgA deficiency
  - Hyper-IgM Syndrome
Hyper-IgM Syndrome

- Patients make normal (or even increased) amounts of IgM
- But can’t make IgG, IgA, or IgE!
- X-linked in most cases
- Patients also have a defect in cell-mediated immunity
- Patients have recurrent bacterial infections and infections with intracellular pathogens (Pneumocystis jiroveci)
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    • Common variable immunodeficiency
    • Isolated IgA deficiency
    • Hyper-IgM Syndrome
    • DiGeorge Syndrome
DiGeorge Syndrome

- Developmental malformation affecting 3rd and 4th pharyngeal pouches
- Thymus doesn’t develop well
- Patients don’t have enough T cells
- Infections: viral, fungal, intracellular pathogens
- Patients may also have parathyroid hypoplasia
- Treatment: thymus transplant!
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    • Common variable immunodeficiency
    • Isolated IgA deficiency
    • Hyper-IgM Syndrome
    • DiGeorge Syndrome
    • Severe combined immunodeficiency
Severe Combined Immunodeficiency

- Group of syndromes with both humoral and cell-mediated immune defects
- Patients get all kinds of infections
- Lots of very different genetic defects
- Half of cases are X-linked
- Treatment: bone marrow transplantation
## Immune Diseases Outline

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<tr>
<th>Disease</th>
<th>Transmission</th>
<th>Defect</th>
<th>Clinical stuff</th>
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<tbody>
<tr>
<td>XLA</td>
<td>X-linked</td>
<td>No mature B cells; no Ig</td>
<td>Infant with recurrent bacterial infections</td>
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<tr>
<td>CVID</td>
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<tr>
<td>IgA deficiency</td>
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