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Rheumatic Diseases
Clinical Immunology
IMMUNITY central dogma

Autoimmunity
- Environmental
  * Mimicry
  * Drugs
  * Injury
- Genetic
- Estrogen
- Age

Hypersensitivity
- Type I
- Type II
- Type III
- Type IV

Loss of tolerance

Aquired Immunity
- T cells
  * T helper
  * T cytotoxic
  * T suppressor
- B cells
  * Plasma cells
- Memory cells

Normal Immunity
- Foreign bodies
- Elimination of the foreign bodies

Innate Immunity
- Anatomical barriers
  * Intact skin
  * Mucous membrane
- Physiological barriers
  * pH
  * Temperature
  * O2 tension
  * Lysozymes
  * Interferons
  * Phagocytes

Immunodefeciency

Foreign bodies
- Elimination of the foreign bodies

Persistant Infections
What are **RHEUMATIC DISEASES**

- The term "rheumatism" is still used in colloquial speech and historical contexts, but is no longer frequently used in medical or technical literature.
- There is no longer any recognized disorder simply called "rheumatism". Some countries use the word *Rheumatism* to describe fibromyalgia syndrome.
- Nevertheless, sources dealing with rheumatism tend to focus on **ARTHRITIS**.
- **However**, "non-articular rheumatism", also known as "regional pain syndrome" or "soft tissue rheumatism" can cause significant discomfort and difficulty.
- Furthermore, arthritis and rheumatism between them cover at least 200 different conditions.
BROAD LIST OF RHUMATIC DISEASES

- RA
- SLE
- Sjögren syndrome
- Scleroderma
- Dermatomyositis
- Polychondritis
- Polymyositis
- Polymyalgia rheumatica
- Osteoarthritis
- Septic arthritis
- VASCULITIS

- Sarcoidosis
- Gout, Pseudogout
- Spondyloarthropathy
- Juvenile idiopathic arthritis
- osteoporosis
- Osteomalacia
- Rickets
- Hyperextensible joints
- Marfan`s, Ehler_Danold
- Etc .........
From **Immunological** perspective:

- **ARTHITIDES** include:
  - Rheumatoid arthritis
  - Juvenile Idiopathic arthritis
  - Rheumatic fever
  - Spondyloarthritis
  - Osteoarthritis
- **VASCULITIDES**
- **SYSTEMIC SCLEROSIS**
- **POLYMYOSITIS**
- Systemic Lupus Erythematosus
- **SJÖGREN syndrome**
1) Rheumatoid arthritis

**Autoimmune, TYPE III** of hypersensitivity disease

The **MOST COMMON** inflammatory arthritis.

**INCEDINCE** ≈ 1% worldwide

“Males : **Females**” ratio ≈ 1 : 3

Etiology **not elucidated** 100%

- Genetic factors >> HLA “DR4, DR1”
  >> PTPN22 and STAT4 genes
- Environmental factors
Anatomy of the knee joint

- Quadriceps muscle
- Femur (thigh bone)
- Articular cartilage
- Anterior cruciate ligament (ACL)
- Lateral collateral ligament (LCL)
- Patella (knee cap)
- Posterior cruciate ligament (PCL)
- Meniscus
- Patellar ligament
- Medial collateral ligament (MCL)
- Tibia (shin bone)

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Normal Joint  Vs  Inflamed Joint

Cut-section view of normal knee joint

- Femur
- Synovial fluid
- Patella
- Synovial membrane

Tibia  Cartilage

Cut-section view of knee joint

- Femur
- Synovial fluid
- Patella
- Inflamed synovial membrane

Tibia  Pitted cartilage
Role of type III hypersensitivity

Antigen–antibody complexes form in blood

Immune complexes are deposited on blood vessel wall, complement is activated, and C3a and C5a are released

Neutrophils are attracted by C5a; they release enzymes that destroy the endothelium and red cells escape from within the blood vessels
Rheumatoid arthritis

Pathogenesis

- The major pathology is localized to the joints.
- Synovial membrane become highly vascular.
- Inflammatory cell recruitment:
  - Neutrophiles, macrophages
  - T cells >>> CYTOKINES
- B cells differentiate into antibody secreting cells “Abnormal plasma cells”
- The most common mediators involved are
  * TNF-α
  * IL-1

Both promote ADITIONALY CELL RECRUITMENT & METALLOPROTEINASES production
Rheumatoid arthritis
Pathogenesis

• Antigen-antibody complex >>> INFLAMMATION
• Autoantibodies

1- Rheumatoid factor
   * 75 – 80 % are seropositive
   * Against Fc portion of IgG
   * present in 70% of Sjögren syndrome
   * Present normally in 5 – 10 % “Elderly”

2- Anticitrullinated peptide antibodies (ACPAs)
   * 85 – 95 % are seropositive
   * Against citrullinated joint proteins
   * Cause changes in protein folding
Rheumatoid arthritis

Clinical Feature

• Slow onset over the course of months.
• Hand, wrist, knee and ankle joint mostly.
• Tend to be symmetrical involvement.
• Erosion of cartilage and subchondral bone.
• Morning Stiffness >> edema.
• Generally begin in the small joints and spread to the larger.
• Extra-articular manifestations:
  - Subcutaneous nodules
  - Pulmonary involvement >> -Pleuritis, fibrosis
  - Ocular involvement >> Scleritis
  - MOSTLY occur in seropositive patients
• Felty`s syndrome >> vasculitis, splenomegaly & leulopenia
Rheumatoid arthritis usually affects joints symmetrically (on both sides equally), may initially begin in a couple of joints only, and most frequently attacks the wrists, hands, elbows, shoulders, knees and ankles.
Rheumatoid arthritis

Treatment

- TRADITIONALLY:
  - NSAID, BUT don’t prevent the progression
  - DMARDs
    - Hydroxychloroquine
    - Sulfasalazine
    - Azathioprine

- RECENTLY
  - Anti-TNF drugs >> Infliximab
  - Anti-IL-1 receptor >> Anakinra
  - Anti CD20 >> Rituximab
  - Co-stimulation mediators >> Abatacept
2) Juvenile Idiopathic arthritis

- Juvenile rheumatoid arthritis >> OLD NAME
- The hallmark of JIA is persistent joint swelling in the absence of any defined cause in someone who is 16 years old or younger.
- **Rheumatoid factor** — Negative in 95% of children with JIA, So IDIOPATHIC
- **THREE MEAN TYPES:**
  1) Oligoarticular (pauciarticular) JIA “Oligo means few”
    - Account ≈ 50% of cases
    - Usually involves the knees, ankles, and elbows but smaller joints such as the fingers and toes may also be affected.
    - It is usually not symmetrical
    - ANAs always present
Types of JIA

2) Polyarticular JIA (( 2 MEAN TYPES ))

- Rheumatoid factor –ve polyarticular JIA
  - Polyarthritis accounts for 25 – 30%

- Rheumatoid factor +ve polyarticular JIA
  - It affects less than 5% of patients with JIA

  ✓ Affecting 5 or more joints in the first 6 months
  ✓ “More in females”
  ✓ Usually the smaller joints are affected, knees, hips, and ankles may also be affected.
  ✓ The joints affected are usually symmetrical
  ✓ ANA usually present

3) Systemic JIA \(\approx\) 20%

  ✓ Is characterized by arthritis, fever and a pink rash.
  ✓ Systemic JIA have internal organs involvement and lead to serositis (e.g. Pancarditis).
  ✓ These children have the worst prognosis of all cases.
Autoimmunity
- Environmental
  - Mimicry
  - Drugs
  - Injury
- Genetic
- Estrogen
- Age

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- Type I
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- Type III
- Type IV

Loss of tolerance

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Foreign bodies
- Elimination of the foreign bodies

Innate Immunity
- Anatomical barriers
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- Physiological barriers
  - PH
  - Temperature
  - O2 tension
  - Lysozymes
  - Interferons
  - Phagocytes

NORMAL IMMUNITY

Immunodeficiency

Persistant Infections
Osteoarthritis
Introduction

As we know, normal joint function includes:
- providing friction-free movement
- acting as shock-absorbents

This requires the joints to:
- be elastic
- have high tensile strength
Remember....

- For these functions to be carried out two substances are essential
  - Collagen type 2
  - Proteoglycans
What is osteoarthritis?

-Osteoarthritis is the most common form of joint pathology.
-It mainly affects middle-aged and elderly people (usually begins in one’s 40s)
-Weight-bearing joints are the most affected.
A note...

Yes... osteoarthritis

But... the disease is mainly a degenerative disease with pro-inflammatory cytokines and inflammatory cells involved →

It is termed: Degenerative Joint Disease

D.J.D.
What is the cause of osteoarthritis??

1. Joint Wear-And-Tear
2. Joint Injury Or Overuse
3. Inactivity
4. Excess Body Weight
5. Heredity
Types

- Primary..
  Related to age, does not require a specific cause or a predisposing condition
- Secondary
  Requires a specific cause..
  Like
  1-trauma
  2-abnormal joint...like congenital anomaly
  3-overuse and wear-and-tear (the disease is often seen in football players
Conditions that predispose to osteoarthritis

A-joint disorders:
1. intra-articular fracture
2. previous infective arthritis
3. Rheumatoid or other inflammatory arthritis
4. Osteonecrosis
B-Abnormal stresses
1-malignant fracture
2-chronic overuse
C-Metabolic or endocrine
1-alkaptonuria
2-hemochromatosis
3-gout
D-Neuropathic disorders
1-peripheral neuropathy
2-spinal cord disorders like syringomyelia
Pathogenesis

- With age the proteoglycan content in joint decreases while the water content increases.

- the synthesis of matrix proteins decreases while breakdown increases

- In early stages of the disease, chondrocytes can compensate for the loss

- Later ... they fail to do so and osteoarthritis develops
Remember...

breakdown > synthesis
• The primary change in osteoarthritis is the alteration in chondrocyte activity with resulting change in the composition of the articular cartilage, in particular of proteoglycans............how??
- The disease involves a local low-grade inflammation
- Chondrocytes produce increased levels of TNF-alpha and IL-1 → increased expression of degradative enzymes + inhibition of matrix protein synthesis
Altered chondrocytes metabolism...

# increased production of matrix metalloproteinases (including collagenase and enzymes that degrade proteoglycans),

# decreased synthesis of proteoglycans, alterations in the proportions of various glycosaminoglycans and weakening of the collagen network.
- Genetic factors:
  1-mutations in collagen types 2 genes in some families
  2-mutation of the ADAM12 gene which encodes a protease enzyme.
Clinical features

- deep, aching pain exacerbated by use and relieved by rest
- Morning stiffness and crepitus on movement
- Limp (antalgic gait) when it involves the hip
- Osteophytes compress vertebral arteries and compromise cerebral blood flow.
- Heberden’s nodes
Osteoarthritis (late stage)

Fusiform swelling of joints

Heberden's nodes
Heberden’s nodes are the size of peas and develop on the end joints of the fingers. Bouchard’s nodes develop on the middle joints of the fingers. The bones also become enlarged. The result is pain, redness, and swelling.
Image of the knee joint with arthritis clearly present.
Treatment and prognosis of DJD

• **Treatment**
  - Meds
  - Early prevention and exercise
  - Heat/cold therapy
  - Joint protection
  - Surgery

**Fate:**
Osteoarthritis is a slowly progressive disease
The eventual outcome is the complete destruction of the joint and ultimately surgical intervention is required.
## Clinical Manifestations of Osteoarthritis

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>Usually after age 40</td>
</tr>
<tr>
<td><strong>Commonly affected joints</strong></td>
<td>Cervical and lumbar spine, first carpometacarpal joint, proximal interphalangeal joint, distal interphalangeal joint, hip, knee, subtalar joint, first metatarsophalangeal joint</td>
</tr>
<tr>
<td><strong>Uncommonly affected joints</strong></td>
<td>Shoulder, wrist, elbow, metacarpophalangeal joint</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Pain, stiffness, gelling</td>
</tr>
<tr>
<td><strong>Findings on physical examination</strong></td>
<td>Crepitus, bony enlargement, decreased range of motion, malalignment, tenderness to palpation</td>
</tr>
<tr>
<td><strong>Synovial fluid analysis</strong></td>
<td>Clear fluid, WBC &lt;2000/mm³, normal viscosity</td>
</tr>
<tr>
<td><strong>Radiographic features</strong></td>
<td>Joint space narrowing, subchondral sclerosis, marginal osteophytes, subchondral cysts</td>
</tr>
<tr>
<td><strong>Patterns of presentation</strong></td>
<td>Monoarticular in young adult; pauciarticular, large-joint in middle age; polyarticular generalized; rapidly progressive; secondary to trauma, congenital abnormality, or systemic disease</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Variable, generally slowly progressive</td>
</tr>
</tbody>
</table>
Spondyloarthropathies

Done by Mai alTayeb
Under supervision of Dr Mansour alYazji
• Termed sero-negative spondyloarthropathies
What are they?

- Simply .. they are inflammatory joint diseases of the vertebral column
A more precise definition

• A group of inflammatory polyarthritides in which tests for rheumatic factor are negative and which tend to involve the sacroiliac joints and the spine (spondylitis) as well as peripheral joints.
They include:

- Ankylosing spondylitis
- Reactive arthritis
- Enteropathic arthritis
- Psoriatic arthritis
The Spondyloarthropathies

- Ankylosing Spondylitis
- Psoriatic Arthropathy
- Sacroiliitis
- Juvenile Ankylosing Spondylitis
- Intestinal Arthropathy
  - Ulcerative Colitis
  - Crohns disease
- Reactive Arthropathy
  - Reiter Syndrome
Notes

• The cause is unclear, but there is strong evidence that the initial event involved interaction between genetic factors and environment factors, particularly bacterial infections.
• There’s a strong association with HLA-B27.
• Patients often have uveitis and aortitis.
• The spondyloarthropathies share certain common features, including the absence of serum rheumatoid factor, an oligoarthritis commonly involving large joints in the lower extremities, frequent involvement of the axial skeleton, familial clustering.
Ankylosing spondylitis

Characterized by:

- Sacroiliitis
- Inflammation of the intervertebral discs in the lumbar spine.
- Enthesitis.
- Patients develop calcification of ligamentous insertions, back stiffness, and pain.
Inflamed sacroiliac joint
Etiology and pathogenesis

• The immunologic basis is not understood.
• There’s a strong association with HLA-B27, which suggests a possible role for antigen presentation to T cells in the immunogenesis.
• The prevalence of the disorder closely parallels the frequency of HLA-B27
• HLA-B27 is present in about 80-98% of white patients.
• Patients who are homozygous for HLA-B27 tend to have a more severe form of the disease.

• It is more common in males with a male to female ratio of 3:1

• Age of onset: late teens to age 40
Clinical features

- Back pain: the most common symptom and first manifestation in 75% of patients.
  - Insidious onset of pain over months or years
- Morning stiffness
- Tenderness at tendon insertion due to inflammation (enthesitis)
Typical tender sites include:

• Costosternal junctions
• Spinous process
• Iliac crest
• Greater trochanters
• Ischial tuberosities
• Tibial tubercles
• Heels (Achilles tendinitis or plantar fasciitis)
Extra-articular manifestations

• 25-35% of patients have uveitis
• Cariac problems:
  - Aortitis
  - Aortic valve incompetence,
  - Conduction abnormalities
  - Cardiomegaly
  - Pericarditis
• Inflammation is followed by fibrosis then ossification.
• The condition is self-limiting but in a minority progresses until the spine is fused → bamboo spine.
extra-articular manifestation cont.

- Weight loss
- High ESR
- Diffuse upper lobe fibrosis
Bamboo spine
Diagnosis

• Diagnosis is made through:
  • (a) medical history including symptoms,
  • (b) X-rays, and possibly
  • (c) blood tests for HLA-B27 gene
Treatment options

- pain and stiffness control when it is early diagnosed.
- exercise
- drugs: NSAID, sulfasalazines
- posture management
- surgery
Progressive systemic sclerosis

Fedaa’ El-Nadi
What is scleroderma?

Scleroderma is an autoimmune disease of the connective tissue.
• Thickening and fibrosis.

Scleroderma is characterized by:
   - formation of scar tissue (fibrosis) in the skin and organs of the body.
   This leads to thickness and firmness of involved areas. Scleroderma, when it's diffuse or widespread over the body, is also referred to as systemic sclerosis
Scleroderma

- General
  - increased deposition collagen in interstitium of small arteries and connective tissue.
  - sclerotic skin changes, often multisystem disease
  - prevalence
    - 18-20/million/year
    - 3-4... F>M
    - 30-50 yrs higher incidence..
    - prognosis
      - black worse white
      - men worse women
Etiology and pathogenesis:

Obliterative vasculopathy. ➔ **endothelial vascular injury**..

 triggered by:
  - Granzymes
  - Endothelial specific autoantibodies..
  - Inflammatory cytokines
  - Vasculotropic viruses
  - Reactive oxygen radicals..
  - Inflammation
  - Autoimmunity
    - *Anti-Scl-70*,
    - *Anti-centromere*

Result in fibrosis.
pathogenesis

The development of an anticentromere antibody response in patients with systemic sclerosis require the presence of a polar amino acid at position 26 in the antigen-binding cleft of the HLA-DQB1 molecule.

- Interleukin-2
- interleukin-4,
- interleukin-6,
- and transforming growth factor-β

Increased expression of intercellular adhesion molecule 1 (ICAM-1) on systemic sclerosis
Scleroderma

General • presentation –

Raynaud’s phenomenon •
edema fingers and hands •
skin thickening •

visceral manifestations –

GI tract, lung, hear, kidneys, thyroid •
arthralgias and muscle weakness often –
Raynaud’s phenomenon

- Intolerance to cold..
- Episodic, reversible cold induced vasospasm. That precede other manifestations..
- Digital arteries undergo marked intimal hyperplasia & adventitial fibrosis..
- Severe narrowing of arterial lumen..
- This account for Raynaud’s phenomenon
  
  **Digital PALLOR ➔ CYANOSIS ➔ HYPEREMIA**

  *(WHITE) ➔ (BLUE) ➔ (RED)* –

  Vasoconstriction usually triggered by COLD, emotion –
  Can be tip of nose, not only digits –
WHITE
BLUE
RED
Diffuse scleroderma

Involvement of GIT
• Impaired function of lower esophageal sphincter.. ✓
• Intermittent heartburn.. ✓
• Other esophageal and bowel problems .. ✓

Pulmonary involvement:
• Mortality ??? ✓
• Fibrotic lung disease ✓
• Pulmonary hypertension ✓
• Lead to dyspnea and nonproductive cough ✓

Other systems
• Musculoskeletal system (arthralgia, arthritis & myositis) ✓
• Kidney ✓
• Heart ✓
Scleroderma

- **Treatment**
  - symptomatic
    - calcium channel blockers in Raynaud’s
    - H2 blockers and proton pump inhibitor for reflux
    - NSAIDS and steroids for arthralgias and myalgias
    - Oral glucocorticoid
    - Cyclophosphamide
    - prostacyclin
    - hand rehab
    - intra-arterial reserpine- decreases vasoconstriction>healing
Scleroderma Diagnostic Criteria

• **One major criterion**: scleromatous skin changes proximal to the metacarpal-phalangeal joints

• **Two of three minor criteria**: sclerodactyly, digital pitting scars, bi-basilar pulmonary fibrosis on CXR
Scleroderma
Scleroderma
Polymyositis

Autoimmune inflammatory muscle disease.. characterized by injury and death of muscle cells that result in severe weakness.

Auto antibodies reactive with tRNA synthetase (Anti-Jo-1)

Also auoreactive CD8+ T cytotoxic cells
Pathogenesis

*Immune* mediated process triggered by *environmental* factors in *genetically* susceptible individuals
Polymyositis and Dermatomyositis

- Proximal muscle weakness and neck extensor muscle also respiratory & oropharyngeal muscles.
- Muscular atrophy (late)
- Nonsuppurative inflammation of skeletal muscle
- 5 cases per million per year
- 2:1 female:male
- Age 40-60, but a pediatric variant of 5-15 year old
Fatigue in

Walking –
Climbing Stairs –
Standing up –
Combing hair –
Reaching above shoulder –
Muscle tendersnessness (uncommon)
Polymyositis/Dermatomyositis Diagnosis

- Proximal muscle weakness and fatigue
- Elevated serum creatinine kinase
- Myopathic changes on electromyography
- Muscle biopsy with evidence of lymphocytic inflammation

Dx is definitive with all four, probable with three, and possible with two.

Rash accompanies these in dermatomyositis
Cause - unknown

- **Genetic** – HLA DR3, DR5, DR, α-TNF polymorphism
- **Immune** – abnormal T cell activity
- **Infectious** – viral agents, Toxoplasma, Borrelia
- **Drugs** – Hydrea, penicillamine, statin, quinidine, phenylbutazone
- **Silicone breast implants** - anecdotal
Rashes of Dermatomyositis

Gottron’s Papules
Dermatomyositis
Polymyositis and Dermatomyositis: Treatment

• **Steroids** for symptomatic patients
• **Methotrexate** and immunosuppressants for non-responders
• **Iv immunoglobulin** for inflammatory myopathies “very very expensive”
Distinguishing Histologic Features

**Polymyositis**
- inflammation *within* muscle tissue (fascicle)
  
  target = myofiber

**Dermatomyositis**
- inflammation *around* fascicle
- perifascicular atrophy in 90% of children and >50% adults
  
  target = blood vessel
Distinguishing Histologic Features

Polymyositis
- lymphocytic (CD8+ T cell) invasion of non-necrotic (viable) myofiber
- CD4+ T cell

Dermatomyositis
- perifascicular atrophy
- **B cells** and complement deposits
- endomysial CD8+ T cells
- CD4+ T cells
Systemic lupus erythematosus (SLE)
a chronic, a multisystem, multifaceted inflammatory disease that can affect every organ system of the body, including the central and peripheral nervous systems and muscles. (autoimmune connective disorder).

It is in the differential diagnosis for many neurological conditions. Neurologists need to be aware of the various presentations and neurologic complications of SLE.
United States: Approximately 250,000 Americans have systemic lupus. The frequency of SLE varies by race and ethnicity, with higher rates reported among black and Hispanic people. The prevalence of SLE is approximately 40 per 100,000 whites in Rochester, Minnesota, versus 100 per 100,000 Hispanic persons in Nogales, Arizona.6,7

International: Worldwide, the prevalence of SLE varies. Although the prevalence of SLE is high in black persons in the United Kingdom, the disease is rarely reported among blacks who live in Africa.
The natural history of SLE varies from relatively benign disease to rapidly progressive and even fatal disease. SLE often waxes and wanes in affected individuals throughout life, and features of the disease vary greatly between individuals. The disease course is milder and survival rate higher among persons with isolated skin and musculoskeletal involvement than in those with renal and CNS disease. SLE carries an average 10-year survival rate that now exceeds 90%.

Infectious complications related to active SLE and immunosuppressive treatment are now the most common cause of death in early active SLE, and accelerated arteriosclerosis is a key cause of late mortality.
Worldwide, the prevalence of SLE appears to vary by race. However, because of different prevalence rates among people of the same race in different geographical locations, a clear conclusion cannot yet be drawn. Low reported rates of SLE in Africa in contrast to a high prevalence in black women in the United Kingdom suggests the importance of environmental influences. In addition, the influence of race on prognosis has been widely debated. The LUMINA study group examined SLE among black, white, and Hispanic patients in the United States (including Puerto Rico) and reported that both disease activity and poverty predicted higher mortality among racial and ethnic minorities.
Systemic lupus erythematosus is prevalent among young women, with a peak age of onset between the late teens and early 40s and a female-to-male ratio of 9:1.

Women aged 35-44 years with SLE were 50 times more likely to develop myocardial ischemia than healthy women.

SLE is more common in men with Klinefelter disease than in men without the disease, also supporting a hormonal hypothesis.

The prevalence of SLE is highest among women aged 14-64 years. SLE does not have an age predilection in males.
SLE

- Febrile inflammatory multisystemic disease - variable symptomatology
- Most often affected: skin, kidneys, serosal membranes, joints, heart
- Several types of Ab - namely antinuclear Ab
- Formation of immunocomplexes
- Histologically - predominantly necrotizing vasculitis
- LE cells (fagocytosis of hematoxylin bodies - destroyed nuclei of cells) - lab test
Many immune disturbances, both innate and acquired, occur in SLE.

In systemic lupus erythematosus (SLE), many genetic-susceptibility factors, environmental triggers, antigen-antibody responses, B-cell and T-cell interactions, and immune clearance processes interact to generate and perpetuate autoimmunity.
Development of autoantibodies involves a defect in apoptosis that causes increased cell death and a disturbance in immune tolerance. The redistribution of cellular antigens during apoptosis leads to a cell-surface display of plasma and nuclear antigens in the form of nucleosomes. Thus, dysregulated (intolerant) lymphocytes begin targeting normally protected intracellular antigens.
Immune complexes form in the microvasculature, leading to complement activation and inflammation. Moreover, antibody-antigen complexes deposit on the basement membranes of skin and kidneys. In active SLE, this process has been confirmed based on the presence of complexes of nuclear antigens such as DNA, immunoglobulins, and complement proteins at these sites. Serum antinuclear antibodies (ANAs) are found in virtually all individuals with active SLE, and antibodies to native double-stranded DNA (dsDNA) are relatively specific for the diagnosis of SLE.
The pathophysiology of SLE has not been defined fully, although many genes that affect immune function, particularly the human leukocyte antigen (HLA), may augment susceptibility to clinical disease. Most monozygotic (identical) twins are discordant for clinical SLE, strongly suggesting that additional factors, probably environmental, trigger the widespread development of autoimmunity in susceptible individuals.
More than 10 gene loci are known to increase the risk of SLE. Human leukocyte antigens (HLA) reveal that HLA-A1, B8, and DR3 are more common in persons with SLE than in the general population. The presence of the null complement alleles and congenital deficiencies of complement (especially C4, C2, and other early components) are also associated with an increased risk of SLE. Epstein-Barr virus (EBV) that may also perpetuate autoimmunity.
SLE :: Immunological Aspects

**INATE SUSCEPTIBILITY**
- HLA type (DR3/2)
- Immunoregulatory genes (multiple)
- Complement levels
- Hormonal levels

**ENVIRONMENTAL STIMULI**
- UV exposure
- Microbial response
- Drugs

**AUTOIMMUNE PROLIFERATION**
- Hyperactive B-cell/T-cell activation
- High ratio of CD4:CD8 T-cells
- Defective immune complex clearance
- Impaired tolerance

**AUTOANTIBODY PRODUCTION**
- Apoptosis & self exposure
- Self-recognition
- Foreign-Ab cross reaction
Decreased CD4<sup>+</sup>CD25<sup>+</sup> T Cells in Peripheral Blood of Patients with Systemic Lupus Erythematosus

patients with SLE had decreased CD4<sup>+</sup>CD25<sup>+</sup> T cells.

Recent animal studies have shown that CD4<sup>+</sup>CD25<sup>+</sup> T cells play a crucial role in the suppression of the immune response and that depletion of this subset of T cells might lead to development of autoimmune diseases. patients with SLE had statistically lower levels of CD4<sup>+</sup>CD25<sup>+</sup> T cells than did normal controls.
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The association between SLE and C1q. Anti-C1q antibodies are also strongly associated with severe SLE affecting the kidney.
• **Skin** - facial exantema (butterfly) - cheeks+radix of the nose

• **Pleura+pericardium** - serous and fibrinous exsudation - fibrosis

• **Heart** - pericarditis
  - endocarditis Libman-Sacks (verrucous) - nonbacterial thrombotic endocarditis
  - both sides of the valve

• **Kidneys** - various forms of Glnf

• **Joints** - swelling, inflammation

• **Spleen** - thickening of the capsule (serositis)
SLE :: Symptomatology
Typical clinical presentation

- young female, butterfly-shaped exantema of the face
- febrile, joint pain, pleuritic pain, photophobia
- ANCA+
- !!!CAVE!!! frequently atypical symptomatology
- clinical course:
  - progressive - death
  - recurrences and remissions - years or decades
- treatment: steroids, immunosupression
Treatment depends on which organs are affected and how active the inflammation of lupus is. The severity of the lupus is not necessarily the same as the activity of the inflammation. The goal of treatment is to decrease the activity of lupus—that is, to decrease inflammation, which in turn should prevent damage.

If lupus is not very active (sometimes called mild lupus): Nonsteroidal anti-inflammatory - The dose and duration of treatment depend on which organs are affected. Sometimes an immunosuppressive drug such as cyclophosphamide is given to suppress the body's autoimmune attack. Mycophenolate mofetil is an alternative immunosuppressive drug. The combination of a corticosteroid and an immunosuppressive drug is most often used for severe kidney disease or nervous system disease and for vasculitis.
Sjögren’s Syndrome
Sjogren’s Syndrome

- 4 million people in the United States
- Second most common autoimmune Rh disease
- 90% women older than 40
- May also cause:
  - skin, nose, and vaginal dryness
  - may affect other organs of the body, including the kidneys, blood vessels, lungs, liver, pancreas, and brain
Sjogren’s Syndrome

• Sjogren's syndrome is an autoimmune disease.

• This particular autoimmune illness features inflammation in certain glands of the body.
  – lacrimal glands
  – salivary glands, including the parotid glands
Primary Vs Secondary SS

- Primary if not associated with other connective tissue disease.
  Could be secondary to rheumatoid arthritis, systemic lupus erythematosus, or scleroderma

- Primary: “sicca syndrome” HLA-DR3
- Secondary: with RA, SLE, etc. HLA-DR4
- R-factor + in 90% percent of cases.
- Causes still unknown.
Sjogren’s Syndrome

- Keratoconjunctivitis sicca (dry eyes)
- Xerostomia (dry mouth)
- B cell lymphoma in 1%
- Pseudolymphoma in 10%
- May also cause:
  - skin, nose, and vaginal dryness
  - may affect other organs of the body, including the kidneys, blood vessels, lungs, liver, pancreas, and brain
Sjogren’s Syndrome

xerostomia and xerophthalmia
Autoimmunity:

Sjogren's syndrome is typically associated with antibodies against a variety of body tissues (autoantibodies).

- ANA
- SS-A and SS-B
- rheumatoid factor
- thyroid antibodies
Immunohistologic analysis of salivary gland lymphoid cell infiltrates in exocrine glands in SS shows:

• T cells with fewer B cells.
• Macrophages, and mast cells.
• Adhesion molecules, including (LFA-1).
• Expression of the mucosal lymphocyte integrin and its ligand, E cadherin, suggests a mucosal origin of a portion of the infiltrating cells.
There is an aberrant and differentiated expression of HLA-DR/DP/DQ molecules on acinar and ductal epithelial cells, presumably due to local production of interferon-$\gamma$ by activated T cells. Most T cells in the lymphocytic infiltrates are CD4$^+$ helper T cells with a CD4/CD8
Prognosis

- *Sjögren’s* can damage vital organs of the body with symptoms that may plateau, worsen, or go into remission. Some people may experience only the mild symptoms of dry eyes and mouth, while others go through cycles of good health followed by severe disease. Many patients are able to treat problems symptomatically. Others are forced to cope with blurred vision, constant eye discomfort, recurrent mouth infections, swollen parotid glands, hoarseness, and difficulty in swallowing and eating. Debilitating fatigue and joint pain can seriously impair quality of life.
Treatment of patients with Sjogren's syndrome is directed toward the particular areas of the body that are involved and complications, such as infection.
Treatment of patients with Sjogren's syndrome is directed toward the particular areas of the body that are involved and complications, such as infection.