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Programme: M.Sc., Biomedical Science

Course Code: BM35C6
Course Title: Immunology

Unit-V
Overview of Autoimmunity and Transplantation

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Unit V:

Overview of Autoimmunity and Transplantation - Autoimmune disease – Spectrum – organ specific (thyroid diseases, IDDM, pernicious anemia) and non-organ specific (Systemic sclerosis & SLE). Factors governing autoimmune diseases- genetic, hormonal, microbial and non-microbial. Regulatory mechanisms involved in autoimmune diseases- Tolerance – breakdown of tolerance (Modification of auto antigen, Cross-reactions with B cell epitopes, molecular mimicry of T cell epitopes. Transplants –auto, allo and Xeno- immunological complications of transplantation – graft rejection, GVHD –mechanisms – prevention of graft rejection- Immunosuppressant Drugs (Glucocorticoids, Calcineurin inhibitors, Antiproliferative/Antimetabolic agents) and antibodies as immunosuppressant

PRESENTATION: 2

Regulatory Mechanisms in Autoimmune Diseases

- Autoimmune diseases result from the immune system’s failure to recognize self-antigens as non-threatening, leading to an attack on the body's own tissues.
- Central to this failure are the mechanisms of immune tolerance, which, when compromised, can lead to the breakdown of tolerance and subsequent autoimmunity.

1. Immune Tolerance

- **Immune tolerance** refers to the immune system's ability to distinguish between self and non-self, preventing an immune response against the body's own tissues. There are two main types of tolerance:

A. Central Tolerance:

- **Location:** Thymus (for T cells) and bone marrow (for B cells).
- **Mechanism:** Developing lymphocytes that strongly recognize self-antigens undergo apoptosis (negative selection), or are rendered anergic (unresponsive).
- **Result:** Elimination or inactivation of self-reactive T and B cells before they mature and enter the periphery.

B. Peripheral Tolerance:

- **Location:** Peripheral tissues.
- **Mechanism:**
  - **Anergy:** Self-reactive T and B cells that escape central tolerance become functionally inactivated when they encounter antigen without the necessary co-stimulatory signals.
  - **Regulatory T Cells (Tregs):** Specialized T cells (CD4+ CD25+ FoxP3+) suppress immune responses against self-antigens by secreting inhibitory cytokines (e.g., IL-10, TGF-β).
  - **Clonal Deletion:** Apoptosis of self-reactive cells upon repeated activation (activation-induced cell death).
  - **Immune Privilege:** Certain sites (e.g., eyes, brain) limit immune access to prevent damage.

2. Breakdown of Tolerance

- The breakdown of tolerance is a pivotal event in the development of autoimmune diseases. Several mechanisms can lead to this breakdown:

A. Modification of Autoantigens:

- **Mechanism:** Post-translational modifications of self-proteins can create new epitopes that are not recognized as self by the immune system. These neo-epitopes can stimulate an autoimmune response.
- **Example:** Citrullination (conversion of arginine to citrulline) of proteins like vimentin in rheumatoid arthritis, creating novel antigens that trigger immune responses.

B. Cross-Reactions with B Cell Epitopes:

- **Mechanism:**

B cells that recognize modified or cryptic epitopes on self-proteins may become activated by foreign antigens that share similar epitopes (molecular mimicry). These activated B cells can then produce autoantibodies against self-antigens.

- **Example:**

B cells recognizing modified DNA or RNA structures in systemic lupus erythematosus (SLE) produce autoantibodies that contribute to disease pathology.

C. Molecular Mimicry of T Cell Epitopes:

- **Mechanism:**

Pathogens can express antigens that resemble self-antigens. When T cells recognize these pathogen-derived peptides, they may cross-react with similar self-peptides, initiating an autoimmune response.

- **Example:**
  - **Rheumatic Fever:** Streptococcal M protein shares structural similarity with heart tissue, leading to cross-reactive T cell responses and cardiac damage.
  - **Multiple Sclerosis:** Certain viral or bacterial proteins may mimic myelin basic protein, leading to T cell-mediated attack on myelin in the central nervous system.

D. Epitope Spreading:

- **Mechanism:**

Initial immune response against a specific epitope of an autoantigen leads to the release of additional self-antigens, exposing new epitopes and broadening the immune attack.

- **Example:**

In SLE, initial attack on a specific nuclear antigen can spread to other nuclear components, expanding the autoimmune response.

E. Release of Sequestered Antigens:

- **Mechanism:**

Self-antigens that are normally hidden from the immune system (e.g., inside cells or immune-privileged sites) can be released following tissue damage or infection, leading to an immune response.

- **Example:**

Trauma to the eye can release intraocular proteins, potentially leading to autoimmune uveitis.

F. Defects in Regulatory T Cells (Tregs):

- **Mechanism:**

Tregs play a crucial role in maintaining tolerance. Deficiency or dysfunction of Tregs can lead to unrestrained immune responses against self-antigens.

- **Example:**

Mutations in the FoxP3 gene result in a lack of functional Tregs, causing immune dysregulation and polyendocrinopathy syndrome (IPEX).

G. Inflammatory Environment:

- **Mechanism:**

Chronic inflammation can upregulate co-stimulatory molecules and cytokines, breaking tolerance and activating autoreactive T and B cells.

- **Example:**

Infections or tissue damage can create an inflammatory milieu that promotes autoimmunity, such as in Type 1 diabetes or rheumatoid arthritis.

3. Clinical Examples of Autoimmune Diseases and Breakdown Mechanisms

A. Type 1 Diabetes Mellitus (IDDM):

- **Mechanism:**

  Molecular mimicry and inflammatory destruction of pancreatic beta cells by CD8+ T cells.

- **Result:**

  Loss of insulin production, hyperglycemia.

Symptoms of Diabetes Type-1

Feeling very weak & hungry

Increase in frequency of urination

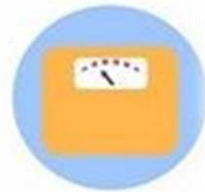
Blurred vision

Excessive thirs

Mood fluctuations

Nocturnal enuresis (bed-wetting) in children

Vaginal infections



Weight loss

B. Systemic Lupus Erythematosus (SLE):

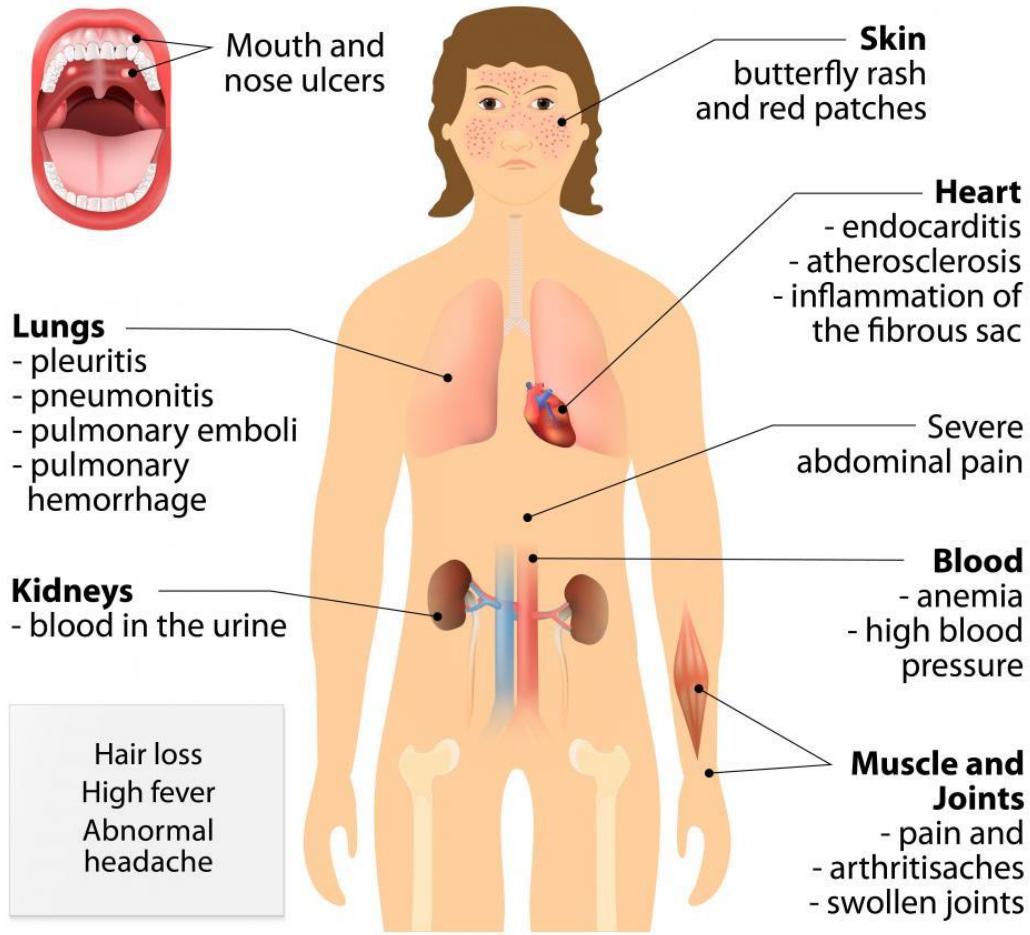
- **Mechanism:**

Defective clearance of apoptotic cells leads to the presentation of nuclear antigens, driving autoantibody production and immune complex formation.

- **Result:**

Multi-systemic inflammation and tissue damage.

Systemic lupus erythematosus



C. Multiple Sclerosis (MS):

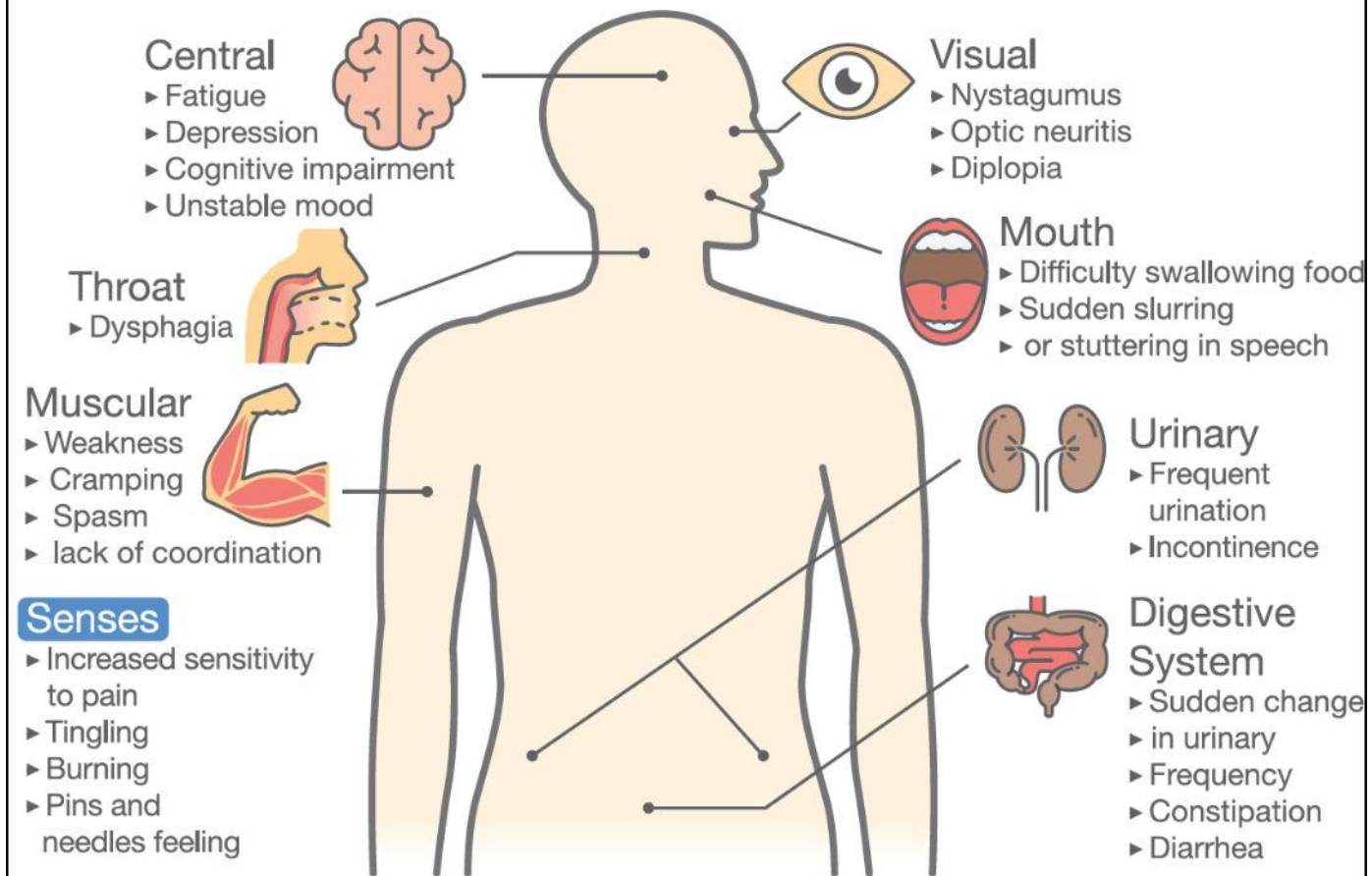
- **Mechanism:**

Molecular mimicry and T cell-mediated destruction of myelin in the central nervous system.

- **Result:**

Demyelination, neuronal damage, and neurological deficits.

Main symptoms of Multiple Sclerosis



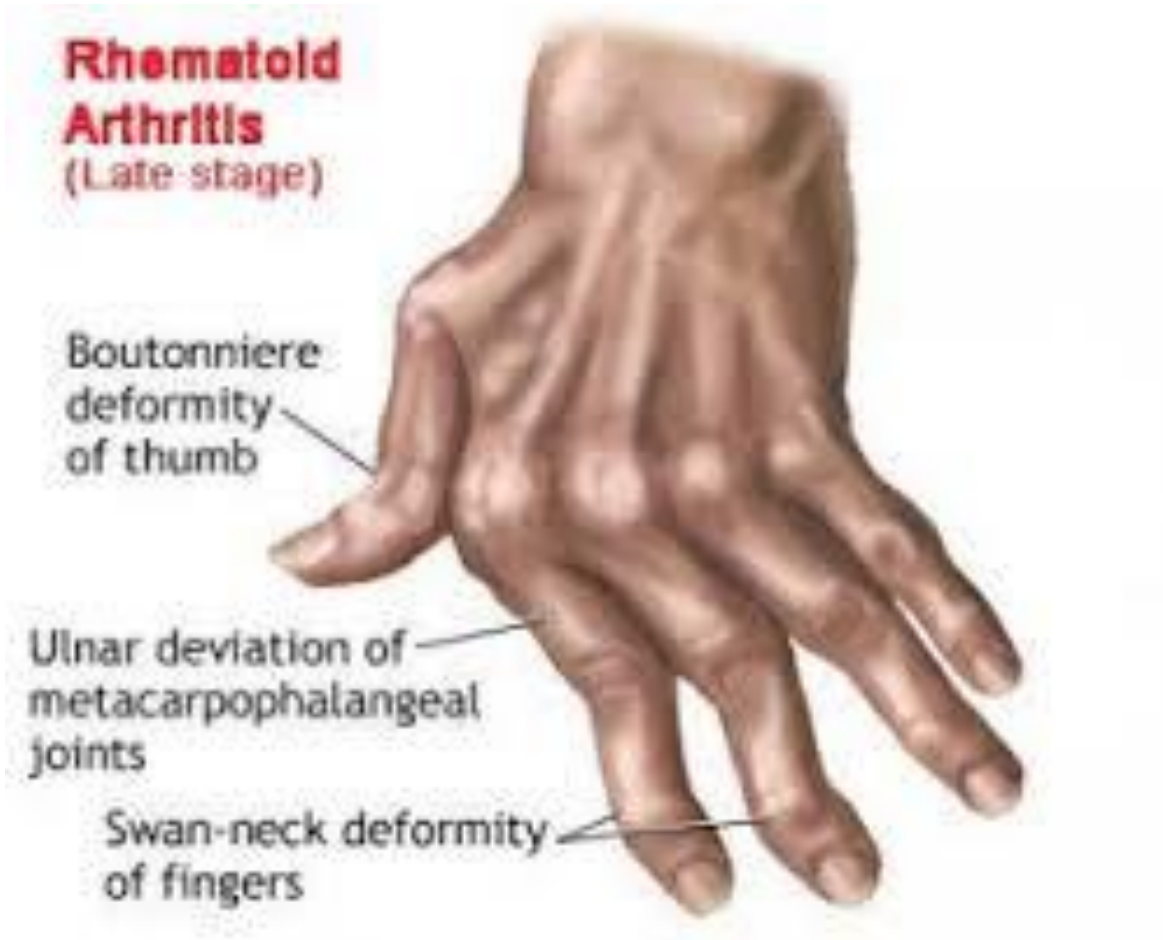
D. Rheumatoid Arthritis (RA):

- **Mechanism:**

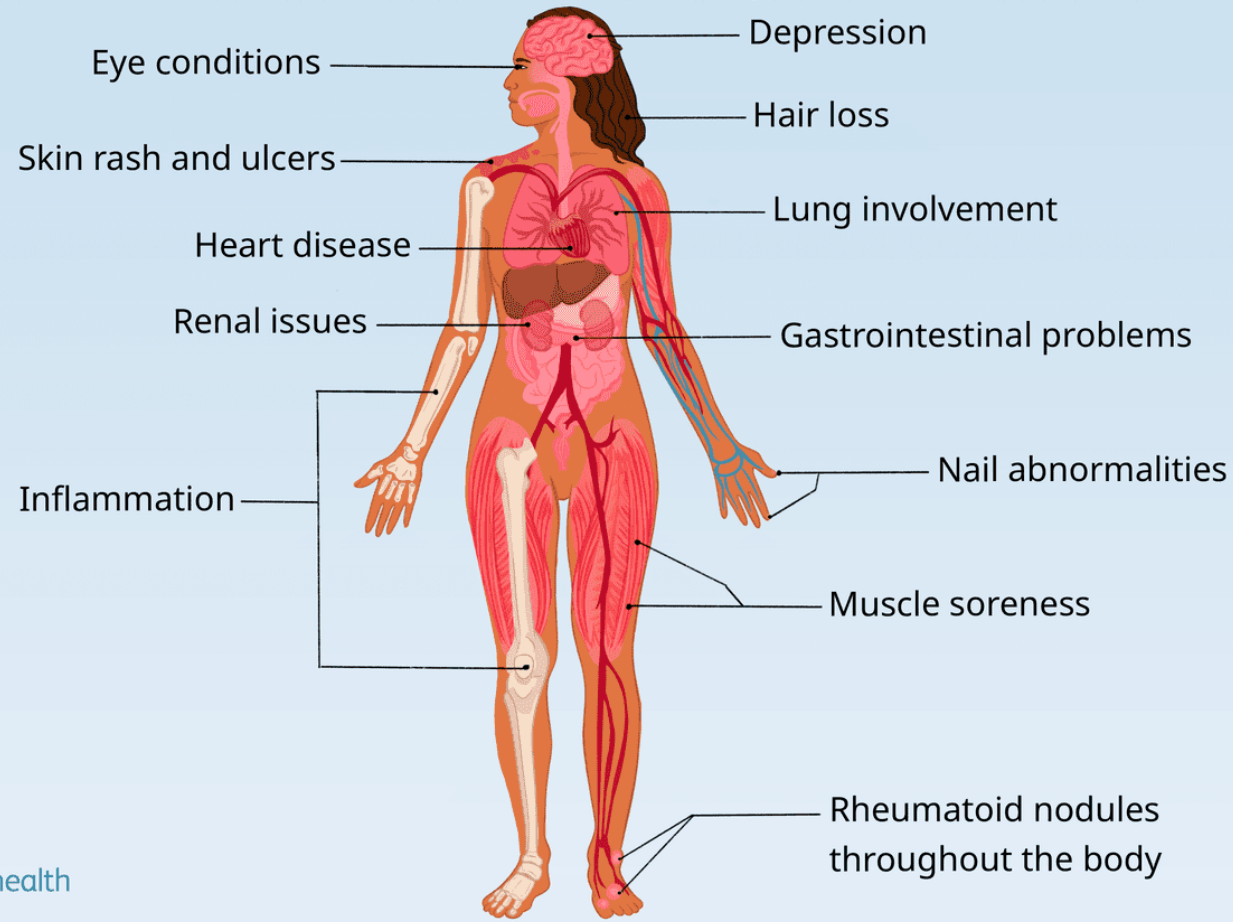
Citrullination of proteins and formation of immune complexes in joints, leading to chronic inflammation and joint damage.

- **Result:**

Joint pain, swelling, and progressive disability.


Rhematoid
Arthritis
(Late stage)
Boutonniere
deformity
of thumb
Ulnar deviation of
metacarpophalangeal
joints
Swan-neck deformity
of fingers

How Rheumatoid Arthritis Affects the Entire Body



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4. Therapeutic Approaches Targeting Tolerance Restoration

A. Immunosuppressive Drugs:

- **Corticosteroids:** Reduce inflammation and immune responses.
- **Calcineurin Inhibitors:** Suppress T cell activation.

B. Biologic Therapies:

- **TNF Inhibitors (e.g., Infliximab):** Reduce inflammation in diseases like RA.
- **B Cell Depletion (e.g., Rituximab):** Target B cells to reduce autoantibody production.

C. Tolerance Induction Strategies:

- **Antigen-Specific Immunotherapy:** Desensitization to specific autoantigens.
- **Regulatory T Cell Therapies:** Enhancing Treg function to restore tolerance.

D. Targeting Inflammatory Pathways:

- **Cytokine Inhibitors (e.g., IL-6 inhibitors):** Reduce inflammation by blocking pro-inflammatory cytokines.

ACKNOWLEDGEMENT

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- Thanks are due to all the original contributors and entities whose pictures were used to create this presentation.