ZAPOROZHZHIAN STATE MEDICAL UNIVERSITY

The department of pathological anatomy and forensic medicine with basis of law

Diseases of immune system

Lecture on pathomorphology
for the 3-rd year students

Pathology of the immune system

- Reactions of hypersensitiveness
- Autoimmune diseases
- Immunodeficiency syndromes
- Amyloidosis
- Tumors of the lymphatic system

Autoimmune diseases

- Autoimmunity it is an immune reaction against "self AG".
- Auto-AB can be formed in response to injured, anti- genetically altered tissues

Classification of autoimmune diseases

- *Organospecific - single organ* (or *single cell) type disorders* - specific immune reactions directed against one particular organ or cell type:
- Hashimoto's thyroiditis
- Autoimmune hemolytic anemia
- Autoimmune gastritis at pernicious anemia
- Autoimmune thrombocytopenia
- Insulin-dependent diabetes mellitus
- Myasthenia gravis
- Graves' disease
- Chronic active hepatitis

- *Multisystem diseases,* characterized by lesions in many organs, associated usually with a multiplicity of auto-AB or cell-mediated reactions, or both.
- Systemic Lupus Erythematous (SLE)
- Rheumatoid Artritis (RA)
- Sjogren's syndrome
- Reiter's syndrome
- Polymyositis-dermatomyositis
- Systemic sclerosis (scleroderma)
- Polyarteritis nodosa

Self-tolerance

- Immune tolerance is defined as a state in which the individual is incapable of developing an immune response against specific AG.
- *Self-tolerance refers to lack of immune responsiveness to the individual's own tissue AG.*

Self-tolerance

- Protection from self "protectors." Deletion of auto-reactive clones appears to be the major mechanism of self-tolerance in T cells.
- *Tolerance of self-reactive T cells is extremely important for prevention of autoimmune diseases.* In contrast to T-cell tolerance, B- cell tolerance is maintained largely by clonal anergy. Because most self AG are T-dependent, auto-AB formation may be prevented by tolerance of either specific B-cells or the relevant T-helper cells.
- Lymphocytes (T and B) that "leak" through the barriers of clonal deletion are restrained by suppressor mechanisms.

Mechanisms of autoimmune disease

- Breakdown of one or more of the mechanisms of self-tolerance can unleash an immunologic attack on tissues that leads to the development of autoimmune diseases, although immunocompetent cells, genetic factors and infectious agents are involved in mediating the tissue injury.

Mechanisms of autoimmune disease

- Autoimmunity results from multiple factors, including susceptibility genes that may interfere with self-tolerance and environmental triggers (inflammation) that promote lymphocyte entry into tissues, activation of lymphocytes, and tissue injury

1. Loss of Self-Tolerance

I. Bypass of T-Helper Tolerance.

- AB responses against most self-AG require collaboration between hapten-specific B cells and carrier-specific T-helper. Mechanisms:

  Modification of the Molecule

  Cross Reactions

  Polyclonal Lymphocyte Activation

II. Imbalance of T- Suppressor-Helper Function.

Any loss of suppressor T-cells function will contribute to autoimmunity and excessive T-cell help may drive B-cells to extremely high levels of auto- AB production.

2. Genetic Factors in Autoimmunity proved by:

1. Familial clustering of human autoimmune diseases such as systemic lupus erythematosus, autoimmune hemolytic anemia, and autoimmune thyroiditis.
2. Linkage of several autoimmune diseases with HLA, especially class II AG.
3. Induction of autoimmune diseases in transgenic rats. In humans, HLA-B27 is strongly associated with certain autoimmune diseases such as ankylosing spondylitis.

3. Microbial Agents in Autoimmunity

- Bacteria, mycoplasmas, and viruses, have been implicated in triggering autoimmunity.
- Microbes may trigger autoimmune reactions by ways:

  microbial AG and auto-AG may become associated to form immunogenic units and bypass T-cell tolerance;

  viruses (Epstein Barr Virus) and bacterial products are non-specific polyclonal B-cell mitogens and may induce formation of auto-AB;

  infection may result in loss of suppressor T-cell function.

- Viruses and other microbes, particularly certain bacteria (streptococci and *Klebsiella)* organisms, may share cross-reacting epitopes with self AG.

IMMUNODEFICIENCY DISEASES

The immunodeficiency's can be subdivided into:

primary diseases of genetic origin

secondary to some underlying disorder

- acquired immunodeficiency syndrome.

Primary immunodeficiency states

- It is inadequacy of immune answer because of an innate defect in the immune system (defect of histogenesis of immunocytes, violation of thymus embryogenesis or regulation of the immune system).
- **They characterized by:**
  - early development (recurrent infections in childhood),
  - relatively uncommon,
  - they are often devastating,
  - the infections are often fatal.

X-Linked Agammaglobulinemia — Bruton's Disease

- It is a failure of pre-B cells to differentiate into mature B cells.
- Clinical recognition - after six months of age. Recurrent bacterial infections such as pharyngitis, sinusitis, otitis media, bronchitis, and pneumonia call attention to the underlying immune defect. The causative organisms are *Haemophilus influenzae, Streptococcus pyogenes, Staphylococcus aureus,* or the pneumococci.
- Most viral, fungal, and protozoal infections are handled normally by cell-mediated mechanisms.

- Characteristics of the classic form of this disease:

B-cells are absent or remarkably decreased, and the serum levels of all classes of immunoglobulins are depressed.

Pre-B cells are found in normal numbers in bone marrow.

Germinal centers of lymph nodes, Peyer's patches, the appendix, and tonsils are under-developed or rudimentary.

Remarkable absence of plasma cells throughout the body.

T cell-system and cell-mediated reactions are entirely normal.

Thymic Hypoplasia (DiGeorge's Syndrome

- It is a lack of thymic influence on the immune system. The thymus is usually rudimentary and T-cells are deficient or absent. They are similarly depleted in the thymus-dependent areas of the lymph nodes and spleen.
- Infants with this defect are extremely vulnerable to viral, fungal, and protozoal infections. The B-cell system and serum immunoglobulins are entirely un-affected.

Severe Combined Immunodeficiency (Swiss-Type Agammaglobulinemia)

- It represents a constellation of syndromes all having in common variable defects in both humoral and cell-mediated immune responses

- Variety of clinical features:

marked lymphopenia with a deficiency of both T- and B-cells

normal numbers of B cells, which are non- functional owing to lack of T-helpers.

normal numbers of circulating lymphocytes that bear the cell surface markers of very immature intra thymic T-cells

thymus is hypoplastic and fetal in type, or it may be absent.

Lymph nodes are difficult to find, markedly reduced in size. They lack both germinal centers, with B-cells, and the para-cortical T-cells. The lymphoid tissues of the tonsils, gut, and appendix are also markedly hypoplastic.

Isolated Deficiency of Immunoglobulin A

- It is the commonest of all the primary immunodeficiency diseases (1/700).

Both serum and secretory IgA are deficient

most persons are asymptomatic,

some present with a variety of symptoms: respiratory infections, chronic diarrhea, and atopic disorders such as asthma,

there is an association with autoimmune

diseases,

IgA deficiency may be familial or acquired in association with toxoplasmosis, measles, or some other virus infection,

The pathogenesis of IgA deficiency seems to involve a block in the terminal differentiation of IgA-secreting B-cells.

When transfused with blood containing normal levels of IgA, some of these patients develop severe, sometimes fatal, anaphylactic reactions.

SECONDARY IMMUNODEFICIENCIES

- It is acquired inadequacy of immune answer because of fatigue or damage of the normally formed immune system.

SECONDARY IMMUNODEFICIENCIES

- **Main reasons of development:**

Infecting HIV-virus with development of AIDS.

Ionizing irradiation or incorporation of radionuclide.

Protracted and un-reasonable treatment by:

cytostatics,

immune-depressants,

corticosteroid hormones,

surplus radial therapy

Tumors of the lymphatic system

Infectious diseases with the defeat of lymphocytes and macrophages (cytomegalovirus and herpetic infections, hepatitis B, other).

Excessive loss of immune proteins through kidneys and intestine.

Violation of functions of immune proteins at

- hepatic insufficiency and diabetes mellitus.

Violation of synthesis of immune proteins at starvation (insufficiency of albumen, iron, zinc, irreplaceable amino acid).

Involutive changes in the organs of the immune

- system in old age after 75 years.

Temporal immune insufficiency at new-born because of insufficient of immune protein synthesis.

Amyloidosis

- Amyloid is an abnormal proteinaceous substance that is deposited between cells in many tissues and organs of the body in a variety of clinical disorders

Chemical Nature of Amyloid

- Two major chemical classes of amyloid have been identified:

  composed of immunoglobulin light chains called AL (amyloid light chain), it is associated with B-cell dyscrasias and is produced by immunoglobulin-secreting cells.

  a unique non-immunoglobulin protein designated AA (amyloid-associated), it is derived from a larger precursor protein in the serum called SAA (serum amyloid- associated protein). AA protein is the major component of the amyloid deposited secondary to chronic inflammatory diseases

I. Clinical setting:

Immunocyte dyscrasias with amyloidosis (primary amyloidosis): Multiple myeloma and other monoclonal B-cell proliferations

Reactive systemic amyloidosis (secondary amyloidosis): Chronic inflammatory conditions

Hemodialysis-associated amyloidosis: Chronic renal failure

Hereditary amyloidosis: (1) Familial Mediterranean fever; (2) Familial amyloidotic neuropathies

Senile cardiac

Senile cerebral (Alzheimer's disease)

Endocrine (e.g., medullary carcinoma of thyroid)

II. Anatomic distribution:

- 1. Systemic (Generalized)
- 2. Localized

III. Chemical composition of amyloid :

- 1. AL
- 2. AA
- 3. SAA

Diagnostic features of amyloidosis

1. Small amounts are not recognized until the surface of the cut organ is painted with iodine and sulfuric acid. This yields mahogany brown staining of the amyloid deposits.
2. When amyloid accumulates in larger amounts, frequently the organ is enlarged, and the tissue is gray with a waxy, firm consistency.

Diagnostic features of amyloidosis

1. Histologically, the deposition begins between cells, often closely adjacent to basement membranes. In time the depositions surround and destroy the native cells.
2. The histologic diagnosis of amyloid is based almost entirely on its staining characteristics. The most commonly used staining technique is Congo red, which under ordinary light imparts a pink or

Amyloidosis of the kidney

- is the most common and the most serious involvement in the disease. Grossly, the kidney may appear un-changed;or it may be abnormally large, pale, gray, and firm *(Big white amyloid kidney);* or it may be reduced in size.
- Microscopically, the amyloid deposits are found in the glomeruli, but they are also present in the interstitial peritubular tissue as well as in the walls of the blood vessels.

Amyloidosis of the spleen

- often causes moderate
- or even marked enlargement (200 to 800 gm). The deposits may be virtually limited to the splenic follicles, producing tapioca-like granules on gross examination *("sago spleen"),* or the involvement may affect principally the splenic sinuses and extend to the splenic pulp, forming large, sheet-like deposits *("lardaceous spleen").* In both patterns, the spleen appears firm in consistency and often reveals on the cut surface, the pale, gray, waxy deposits.

Amyloidosis of the liver

- Histologically, the deposits appear first in the space of Disse and then progressively enlarge to the hepatic parenchyma and sinusoids. The trapped liver cells are literally squeezed to death and are eventually replaced by sheets of amyloid.

Amyloidosis of the heart (senile amyloidosis)

- Macroscopic characteristic: gray-pink, dewdrop-like subendocardial elevations, particularly in the atrial chambers.

- Amyloidosis of the endocrine organs, particularly of the adrenals, thyroid, and pituitary, is common in advanced systemic distributions. The amyloid deposition begins in relation to stromal and endothelial cells and progressively encroaches on the parenchymal cells.