Ministry of Health of the Republic of Belarus
Educational Institution
“Gomel State Medical University”

Department of Pathological Anatomy

Author:
Grigorii V. Tishchenko, Associate Professor of the Department of Pathological Anatomy, Candidate of Medical Sciences (Ph.D. in Medicine)

METHODICAL GUIDELINES

for conducting a practical class
in the academic discipline “Pathological Anatomy”
for students
of the 3rd year, Faculty of International Students (instruction in English),
enrolled in the specialty
7-07-0911-01 “General Medicine”

Topic: “Mesenchymal degenerations”

Duration: 3 hours

Approved at the meeting of the Department of Pathological Anatomy
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EDUCATIONAL AND INSTRUCTIONAL GOALS, OBJECTIVES, AND MOTIVATION FOR MASTERING THE TOPIC

Educational Goal:

- To equip students with scientific knowledge regarding stromal-vascular degenerations, as well as the necessary skills and abilities for studying the etiopathogenesis and structural-functional features of stromal-vascular degenerations. This will be achieved by analyzing the general characteristics of the degenerative process and its classification based on the predominant type of metabolic disorder (protein, fat, carbohydrate), the localization of changes (cellular, extracellular, mixed), and the prevalence of the process (systemic and local). This will foster students' understanding of the initial mechanisms underlying the development of pathological processes.

Instructional Goal:

- Within the framework of the educational process for this academic discipline, the student must acquire not only theoretical knowledge, practical skills and abilities in the specialty but also develop their personal potential. They should cultivate qualities of responsibility and patriotism, be prepared to actively participate in the economic, socio-cultural, and public life of the country, recognize the social significance of their future professional activity, understand the norms of medical ethics and deontology, and learn to observe academic and labor discipline. In the course of studying the educational material, students should realize the importance of maintaining a healthy lifestyle and, as an example in the future, when performing professional duties, set an example for those around them and their patients.

Objectives: Upon completion of the practical session, the student must:

***Know*:**

- The causes, mechanisms, and morphological features of typical general pathological processes;
- The etiology, pathogenesis, and morphology of diseases at different stages of their development (morphogenesis), the structural basis of recovery, complications, outcomes, and long-term consequences of diseases, as well as the causes and mechanisms of dying (thanatogenesis).

Be able to:

- Identify major general pathological processes and diseases using histological specimens under light microscopy;
- Diagnose pathological processes and diseases based on the description of macroscopic and microscopic changes in organs and tissues of the body.

Master:

- Basic techniques for working with a microscope;
- Skills in clinical-anatomical analysis;
- The fundamentals of synthetic generalization of morphological diagnostic signs of diseases and their correct interpretation in cause-and-effect relationships.

Motivation for Mastering the Topic:

The vital activity of any tissue occurs as a result of continuous metabolism. In some cases, metabolic disorders cause qualitative changes in tissues or organs, whereby the content of natural metabolites increases in the cell and intercellular substance, or substances of a different chemical or physical composition appear. Such changes are called degeneration. Degeneration is among the most ancient processes in phylogenesis and accompanies many pathological processes and diseases in both children and adults. Thus, the degenerative process is universal and constitutes a general pathological category. It can unfold at various levels of organization of living matter: organ, tissue, cell, and cellular ultrastructures. The multitude of causes (nutritional, infectious and toxic, neuroendocrine disorders, developmental defects of various systems) disrupts the regulatory activity of the central nervous and immune systems, thereby altering the normal metabolism of proteins, fats, carbohydrates, and vitamins.

During the session, students are invited to study the structural-pathogenetic changes in organs and tissues in stromal-vascular dysproteinoses, lipidoses, and carbohydrate degenerations; analyze the morphogenetic aspects of the development of specific types of stromal-vascular degenerations; and pay attention to rare cases of congenital storage diseases.

QUESTIONS

1. Mesenchymal degenerations (dystrophies). Definition. Classification. General mechanisms of development of degenerative processes.
2. Mucoid and fibrinoid swelling. Etiology. Pathogenesis. Morphology. Clinical examples. Outcomes.
3. Hyalinosis. Classification. Etiology. Pathogenesis. Morphology. Clinical examples.
4. Amyloidosis. Classification. Etiology. Pathogenesis. Morphology. Methods of detection and staining. Outcomes.
5. Obesity, cachexia. Definition. Classification. Etiology. Pathogenesis. Morphology. Staining.

COURSE OF THE SESSION

Mesenchymal, also known as **stromal-vascular**, degenerations arise due to metabolic disorders affecting connective tissue. These degenerations are typically observed within the stroma of organs and the walls of blood vessels.

Mesenchymal degenerations reflect **metabolic disturbances** within the connective tissue system, particularly highlighting its trophic (or metabolic) functions. The central event in these degenerations is damage to the trophic transport systems, which leads to a **progressive state of hypoxia**. Due to shared morphogenic pathways, it is possible to observe **multiple types** of degenerative changes simultaneously, and **transitions** from one form of degeneration to another can also occur.

Mesenchymal degenerations can be classified based on the specific metabolic pathways involved, primarily including disruptions in **protein**, **lipid**, and **carbohydrate** metabolism.

Protein mesenchymal degenerations

Protein mesenchymal degenerations include the following types:

1. Mucoid Swelling
2. Fibrinoid Swelling
3. Hyalinosis
4. Amyloidosis

The first three types—mucoid swelling, fibrinoid swelling, and hyalinosis—often represent **sequential stages of connective tissue disorganization**.

These degenerative changes are frequently observed in a variety of diseases, with a notable prevalence in **rheumatic conditions**.

Mucoid swelling

Mucoid change (or mucoid degeneration) is characterized by the accumulation of **mucin-like substances** within the fibers of tendons, ligaments, and fibrocartilage. This process is known as mucoid swelling, which involves a **superficial** and **reversible** disorganization of connective tissue.

Mucoid swelling is commonly observed in the **walls of arterioles and arteries**, **heart valves**, **renal glomeruli**, and the **parietal endocardium**, particularly in the context of infectious rheumatic diseases.

A key histological feature of mucoid swelling is **metachromasia** — a phenomenon where certain tissue components, when stained with a single dye, exhibit different colors than that of the dye solution itself.

While mucoid swelling is reversible, if the underlying pathological factors persist, it **can progress** to an irreversible state known as fibrinoid swelling.

Fibrinoid swelling

Fibrinoid swelling represents a **deep** and **irreversible** disorganization of connective tissue. This process involves the destruction of the fundamental matrix and connective tissue fibers, accompanied by a marked **increase in vascular**

permeability. This allows the release of coarse plasma proteins, primarily *fibrinogen*, which subsequently transforms into *fibrin*. Eventually, this process results in the formation of a distinctive substance known as *fibrinoid*, composed of glycoproteins.

Fibrinoid swelling is an irreversible process that often culminates in **fibrinoid necrosis**, **hyalinosis**, or **sclerosis**, leading to significant dysfunction of the affected organ, potentially resulting in organ insufficiency.

This type of degeneration is commonly associated with infectious, allergic, autoimmune, and rheumatic diseases.

Microscopically, fibrinoid swelling is characterized by the **homogenization of collagen fibers** and the depolymerization of glycosaminoglycans within the connective tissue matrix. Unlike mucoid swelling, **metachromasia is not observed** in this condition.

Hyalinosis

Hyalinosis is characterized by the accumulation of **translucent**, **dense** masses in tissues, resembling hyaline cartilage. This condition typically arises as a consequence of fibrinoid swelling, plasmorrhagia, sclerosis, or necrosis.

The formation of hyaline involves the **destruction of fibrous structures** within the tissue, followed by their **impregnation with fibrin** and other plasma components, such as globulins, beta-lipoproteins, and immune complexes.

There are two primary types of hyalinosis:

1) Hyalinosis of **connective tissue**

2) Hyalinosis of **blood vessels**, primarily affecting arteries

Both types of hyalinosis can present in either a widespread (**general**) or **localized** manner.

Types of Hyaline

Hyaline formation in tissues can be classified into three types based on the underlying mechanisms and associated conditions:

1) **Simple Hyaline**

- *Cause*: Angiopathic disorders, primarily hypertension.
- *Mechanism*: Infiltration mechanism.
- *Characteristics*: Hyaline deposition primarily affects medium-sized vessels.

2) **Lipohyalin**

- *Cause*: Diabetes mellitus.
- *Mechanism*: Combination of infiltration and transformation mechanisms.
- *Characteristics*: Hyaline deposition primarily affects small-sized vessels.

3) **Complex Hyaline**

- *Cause*: Autoimmune diseases.
- *Composition*: Consists of proteins combined with immunoglobulins.

Clinical Implications of Hyalinosis

1) **Hyalinosis in Hypertension and Diabetes**:

1) **Hypertension**: Hyalinosis primarily damages *medium-sized vessels*, leading to vascular stiffness and impaired function.

2) **Diabetes**: Hyalinosis predominantly affects *small-sized vessels*, contributing to microvascular complications.

2) **Hyalinosis of Connective Tissue**:

Hyalinosis of connective tissue typically develops as a **result of fibrinoid swelling**, particularly in **rheumatic diseases**. This process leads to significant structural changes in the affected organs, including deformation, wrinkling, and atrophy. The prognosis is generally unfavorable, although in rare cases, partial resorption of hyaline masses may occur.

Amyloidosis

Amyloidosis refers to a group of diseases characterized by the **abnormal deposition** of proteins, known as amyloid fibrils, within tissues. These fibrils accumulate in the stroma of organs and the walls of blood vessels, forming a complex glycoprotein called amyloid, which is not normally present in the body.

There are over **36 different types of amyloidosis**, each resulting from the misfolding of a specific protein. These types are categorized as follows:

1) **Localized Forms**: 19 types

2) **Systemic Forms**: 14 types

3) **Dual Forms**: 3 types, which can present as either localized or systemic

The misfolding of these proteins can be triggered by **genetic factors** or **acquired environmental influences**, leading to the development of amyloidosis.

Epidemiology of amyloidosis

Amyloidosis is a rare condition with a combined estimated prevalence of 30 per 100,000 people. The median age at diagnosis is **64 years**.

AL Amyloidosis (Light Chain):

- The most common type in developed countries, with an incidence of 12 cases per million persons per year.

AA Amyloidosis (Inflammation-Related):

- The most prevalent form in developing countries. It often arises as a complication of chronic infections, such as tuberculosis, osteomyelitis, and bronchiectasis.
- In Western countries, AA amyloidosis is most commonly associated with conditions like rheumatoid arthritis, inflammatory bowel disease, and psoriasis.

Wild-Type Transthyretin (ATTR) Amyloidosis:

- Found in approximately 25% of elderly individuals at postmortem examination.

The most common types of amyloidosis include:

- **AL** Amyloidosis (Light Chain)
- **AA** Amyloidosis (Inflammation-Related)
- **Aβ2M** Amyloidosis (Dialysis-Related)
- Hereditary and Age-Related Amyloidosis (including **ATTR** and familial amyloid polyneuropathy)
- **AF** Amyloidosis (Fetal)

Classification of amyloidosis

Historically, classification systems for amyloidosis were based primarily on clinical factors. Until the early 1970s, the prevailing belief was that amyloidosis involved a single, uniform substance.

Several descriptive classification systems emerged, focusing on the organ distribution of amyloid deposits and associated clinical findings.

Most early classification systems categorized amyloidosis into:

1) **Primary Amyloidosis** (Idiopathic): Cases where no associated clinical condition was identified.

2) **Secondary Amyloidosis**: Cases secondary to chronic inflammatory conditions, such as chronic infections or autoimmune diseases.

Some systems also recognized additional categories, including:

- Myeloma-Associated Amyloidosis
- Familial Amyloidosis
- Localized Amyloidosis

Classification of amyloidosis

1) By **causative factor**:

- **primary** arise from a disease with disordered immune cell function, such as multiple myeloma or other immunocyte dyscrasias
- **secondary** (reactive) amyloidosis occur as a complication of some other chronic inflammatory or tissue-destroying disease. Examples are reactive systemic amyloidosis and secondary cutaneous amyloidosis.

2) By **specificity** of amyloid fibril proteins: **AA, AL, AF,** etc.

3) By **prevalence**:

- **systemic** amyloidoses: affect more than one body organ or system. Examples: AL, AA, Aβ2M.
- **localized** amyloidoses: affect only one body organ or tissue type. Examples: Aβ (found in Alzheimer's disease), IAPP (islet amyloid polypeptide in the pancreas), AANF (atrial natriuretic factor in the heart).

4) **Topographically**, based on the predominance of organ or system involvement: cardiopathic, nephropathic, neuropathic, hepatopathic, epinephropathic, mixed, APUD-amyloidosis.

Pathophysiology and Diagnosis

Amyloidoses can be considered protein **misfolding diseases**. The vast majority of proteins that have been found to form amyloid deposits are secreted proteins, so the misfolding and formation of amyloid occurs outside cells, in the extracellular space.

These fibrillar proteins are synthesized by **amyloidoblasts**. The plasma component is blood plasma glycoproteins.

Diagnosis of amyloidosis generally requires **tissue biopsy**. The biopsy is assessed for evidence of characteristic amyloid deposits. The tissue is treated with various stains.

The most useful stain in the diagnosis of amyloid is **Congo red**, which, combined with **polarized light**, makes the amyloid proteins appear **apple-green on microscopy**. Also, **thioflavin T stain** may be used.

Pathophysiology of Amyloidosis

Amyloidoses are considered protein **misfolding diseases**.

Most proteins that form amyloid deposits are secreted proteins, meaning the misfolding and formation of amyloid occur **outside of cells**, in the **extracellular space**.

Amyloid Formation:

1) **Amyloidoblasts**: Cells responsible for synthesizing fibrillar proteins that contribute to amyloid deposits.

2) **Plasma Component**: The amyloid fibrils often include blood plasma glycoproteins.

Diagnosis of Amyloidosis

1) **Tissue Biopsy**: Essential for diagnosing amyloidosis. A biopsy is analyzed for the presence of characteristic amyloid deposits.

2) **Staining Techniques**:

- **Congo Red Stain**: The most useful stain for detecting amyloid. When viewed under polarized light, amyloid deposits exhibit an apple-green birefringence, which is a key diagnostic feature.
- **Thioflavin T Stain**: Another stain that can be used to identify amyloid deposits.

These diagnostic methods help in confirming the presence of amyloid deposits and differentiating amyloidosis from other conditions.

Prognosis in Amyloidosis

The prognosis for amyloidosis varies significantly depending on the type of amyloidosis and the organ systems affected.

1) **AL Cardiac Amyloidosis**: Poor, with a median survival of approximately six months if untreated.

2) **AA Amyloidosis**: Dependent on the underlying disease, the organs involved, and the concentration of serum amyloid A protein. Outcomes improve if the underlying condition is well-managed.

3) **ATTR Amyloidosis** (Including Both Mutant and Wild-Type): Generally better compared to AL amyloidosis. Patients may have a survival of over a decade, especially with appropriate management.

Additional Factors Influencing Survival:

1) **Gender and Age**: Survival time is not significantly associated with gender or age.

2) **Heart Function**: Reduced heart function is associated with a shorter survival time.

Mesenchymal lipidosis

Mesenchymal lipidosis refers to structural changes in the body associated with disruptions in **adipose tissue metabolism** and **fat storage**. This condition also involves abnormalities in the metabolism of cholesterol and its esters, particularly within the walls of major arteries, which is a key feature in the development of **atherosclerosis**.

Stromal fatty infiltration occurs when mature **adipose cells accumulate within the stromal connective tissue**. This differs from intracellular fat deposition, which happens within parenchymal cells during fatty change.

Disruptions in neutral fat metabolism can present either systemically or locally, resulting in either an **increase** or **decrease** in fat content within fat depots.

Increase in Neutral Fat: When neutral fat accumulates excessively in adipose tissue, it leads to a condition known as **obesity**.

Etiological Classification of Obesity

1) **Alimentary Obesity**: Caused by excessive caloric intake relative to energy expenditure.

2) **Cerebral Obesity**: Results from damage to the hypothalamus or other brain regions that regulate appetite and metabolism.

3) **Endocrine Obesity**: Associated with hormonal imbalances, such as in **Cushing syndrome**, which is characterized by prolonged exposure to high levels of glucocorticoids like cortisol.

4) **Hereditary Obesity**: Linked to genetic conditions such as **Von Gierke disease**, where the body is unable to break down glycogen, leading to its storage as fat in the liver and muscles, eventually transforming into adipose tissue.

Classification by Excess Body Weight

Obesity can also be categorized based on the **percentage of excess body weight**:

- I Degree: 20-29% overweight
- II Degree: 30-49% overweight
- III Degree: 50-99% overweight
- IV Degree: more than 100% overweight

Hypertrophic vs. Hyperplastic Obesity

1) **Hypertrophic Obesity**: Characterized by an increase in the volume of existing adipose cells.

2) **Hyperplastic Obesity**: Involves an increase in the number of adipose cells.

Mesenchymal lipidosis

Stromal fatty infiltration commonly affects the **heart** and **pancreas**. The presence of mature adipose cells in the stroma generally does not cause dysfunction. However, in the heart, this infiltration is linked to an increase in adipose tissue within the epicardium. In cases of severe obesity, excessive stromal fatty infiltration of the herat can lead to adverse outcomes, including myocardial rupture, which may result in cardiac tamponade—a life-threatening condition.

A localized increase in adipose tissue is known as **lipomatosis**. This condition is observed in **Dercum's disease**, a rare disorder characterized by multiple painful subcutaneous nodules of fatty tissue (lipomas).

A severe reduction in the quantity of neutral fat throughout the body is termed **cachexia**. This condition is associated with extreme weight loss and muscle wasting, often seen in chronic illnesses.

Atherosclerosis is underpinned by disturbances in **cholesterol metabolism**.

Mesenchymal carbohydrate degeneration

Mesenchymal carbohydrate degenerations are linked to impaired metabolism of **glycoproteins** and **glycosaminoglycans**. These metabolic disruptions lead to structural changes in connective tissue.

1) **Glycoprotein Metabolism**:

Disruptions in glycoprotein metabolism result in the hypersecretion of mucin, causing an excessive accumulation of mucus within the connective tissue.

2) **Glycosaminoglycan Accumulation**:

The accumulation of glycosaminoglycans can lead to congenital enzymopathies, which are disorders caused by defective or deficient enzymes involved in metabolism.

Connective Tissue Mucinosis

Connective tissue mucinosis is associated with the following conditions:

1) Mucoid Degeneration in **Tumors**: Seen in certain tumors such as **myxoma** and **pleomorphic adenoma**.

2) **Neurofibromas** and **Soft Tissue Tumors**: Characterized by mucin accumulation within the connective tissue.

3) Myxomatous Change in **Myxedema**: Occurs in the dermis during myxedema, which is a form of mucous edema associated with hypothyroidism.

4) Myxoid Change in **Ganglion Cysts**: Observed in the synovium of ganglion cysts, commonly found on the wrist.

Outcome:

The process can be reversible if managed early. However, if it progresses, it may lead to colliquation (liquefaction) and tissue necrosis, resulting in the formation of cavities filled with mucus.

INFORMATIONAL AND METHODOLOGICAL PART

MAIN LITERATURE

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2. Klatt, E. C. Robbins and Cotran Atlas of Pathology : [with Student Consult Online Access] / Edward C. Klatt. - third edition. - Philadelphia : Elsevier, 2015. - 587 p. : il.

3. Robbins Basic pathology / [ed. by] Vinay Kumar, Abul K. Abbas, Jon C. Aster. - 9th ed. - [Philadelphia] : Elsevier ; Saunders. - 910 p. : ill., scheme, tab.

ADDITIONAL LITERATURE

1. Sobotta. Atlas of human anatomy. [V. 1]. General anatomy and musculoskeletal system / ed. by F. Paulsen, J. Waschke. - 15th ed. - München : Elsevier. Urban & Fischer, 2011. - 400 p. : ill., col. ill.

2. Sobotta. Atlas of human anatomy. [V. 2]. Internal organs / ed. by F. Paulsen, J. Waschke. - 15th ed. - München : Elsevier. Urban & Fischer, 2011. - 259 p. : ill., col. ill.

3. Sobotta. Atlas of human anatomy. [V. 3]. Head, neck, and neuroanatomy / ed. by F. Paulsen, J. Waschke. - 15th ed. - München : Elsevier. Urban & Fischer, 2011. - 370 p. : ill., col. ill.

4. Weir & Abrahams' imaging atlas of human anatomy / ed.: J. D. Spratt [and oth.] ; consultant eds.: J. Weir, P. H. Abrahams. – 5th ed. - [S.l.] : Elsevier, 2017. - xvi, 263 p. : ill.

NORMATIVE LEGAL ACTS AND DOCUMENTS

1. Order of the Ministry of Health of the Republic of Belarus No. 111 of 06/01/1993 "On further improvement of the pathological service of the Republic of Belarus"

Access mode: http://patan.by/menyu/administrativnyie-proczeduryi.html - The date fccess: 20.03.2022.

ELECTRONIC DATABASES

1. Physician's consultant. Electronic Medical Library = Consultant of the doctor. Electronic medical library [Electronic resource] / Publishing group "GEOTAR-Media", LLC "IPUZ". – Access mode: http://www.rosmedlib.ru/ . – Access date: 03/15/2022.

2. Springer Link [Electronic resource] / Springer International Publishing AG. – Access mode: https:link.springer.com. – Date of access: 03/15/2022.