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

Department of Pathological Anatomy

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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: “Infectious pathology: tuberculosis”

Duration: 3 hours

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EDUCATIONAL AND INSTRUCTIONAL GOALS, OBJECTIVES, AND MOTIVATION FOR MASTERING THE TOPIC

Educational Goal:

- To study the definition, classification, etiology, pathogenesis, morphology, clinical presentation, complications, and outcomes of tuberculosis (TB). To analyze the etiological agent: Mycobacterium tuberculosis (acid-fast bacillus, Koch bacillus), transmission (airborne droplets). To discuss the pathogenesis: inhalation of bacilli → phagocytosis by alveolar macrophages → intracellular survival → delayed-type hypersensitivity (DTH) and cell-mediated immunity (CMI) → formation of granulomas. To describe the primary tuberculosis (Ghon focus): Ghon focus (subpleural caseous nodule) + hilar lymph node involvement = Ghon complex (Ranke complex when calcified). To examine post-primary (secondary, reactivation) tuberculosis: apical localization (Simon foci), caseous necrosis, cavitation, fibrosis. To describe the morphology of the tuberculous granuloma (tubercle): central caseous necrosis, epithelioid histiocytes, Langhans giant cells (horseshoe arrangement of nuclei), peripheral lymphocytes and fibroblasts. To analyze the outcomes of tuberculosis: healing (fibrosis, calcification, encapsulation), progression (cavitation, bronchogenic spread, miliary tuberculosis – millet seed-like lesions in multiple organs), complications (hemoptysis, pleural effusion, empyema, bronchopleural fistula, amyloidosis, cor pulmonale, tuberculous meningitis, Pott disease (spinal TB), lupus vulgaris (cutaneous TB), scrofula (cervical lymphadenitis), genitourinary TB (sterile pyuria). To discuss the relationship between TB and HIV/AIDS (co-epidemic, increased risk of reactivation and dissemination). To examine drug-resistant TB (MDR-TB, XDR-TB) and its pathological features.

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 etiology and transmission of tuberculosis;
- The pathogenesis of primary and post-primary tuberculosis;
- The morphology of the tuberculous granuloma (caseous necrosis, epithelioid cells, Langhans giant cells);

- The components of the Ghon complex;
- The outcomes and complications of tuberculosis (miliary TB, cavitation, fibrosis, calcification, amyloidosis);
- The relationship between TB and HIV/AIDS.

Be able to:

- Identify caseous necrosis and tuberculous granulomas on histological specimens;
- Recognize Langhans giant cells and acid-fast bacilli (Ziehl-Neelsen stain);
- Distinguish primary from post-primary tuberculosis based on macroscopic findings;
- 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:

Tuberculosis remains one of the deadliest infectious diseases worldwide, with approximately 10 million new cases and 1.5 million deaths annually. The emergence of drug-resistant TB and the HIV co-epidemic have further complicated control efforts. Understanding the morphological features of tuberculosis is essential for pulmonologists, infectious disease specialists, pathologists, and public health professionals for accurate diagnosis, treatment, and prevention. Tuberculosis can affect virtually any organ system, making knowledge of its diverse manifestations critical for all clinicians.

QUESTIONS

1. Primary tuberculosis. Definition. Pathogenesis. Morphology. Primary tuberculosis complex. Complications and outcomes. Causes of death.
2. Hematogenous tuberculosis. Definition. Pathogenesis. Classification. Morphology. Miliary tuberculosis. Complications and outcomes. Causes of death.
3. Secondary tuberculosis. Definition. Pathogenesis. Classification. Morphology. Complications and outcomes. Causes of death.

COURSE OF THE SESSION

Tuberculosis (TB) is a chronic infectious disease primarily affecting the lungs, though it can involve any organ or tissue in the human body. This disease is characterized by its widespread prevalence, dual nature of infection, diverse clinical and morphological presentations, and a chronic, wave-like course with periods of exacerbation and remission. The etiological agent is Mycobacterium tuberculosis, with both human and bovine strains being pathogenic to humans.

Transmission of TB occurs through exposure to an infected individual or animal, who releases mycobacteria into the environment. The primary route of infection is via the respiratory tract, although transmission can also occur, albeit less frequently, through the gastrointestinal tract, and rarely through the skin, middle ear, conjunctiva, or placenta. TB manifests in three major pathogenetic and clinical-morphological forms: primary tuberculosis, hematogenous tuberculosis, and secondary tuberculosis.

Primary tuberculosis occurs upon the initial infection with the pathogen, leading to sensitization and immediate hypersensitivity reactions. It is characterized by exudative-necrotic lesions, a propensity for hematogenous and lymphogenous dissemination, and various paraspecific responses such as vasculitis, arthritis, and serositis. While primary TB is predominantly seen in children, there has been a notable increase in cases among adolescents and adults.

Upon entry of Mycobacterium tuberculosis into the host, a complex reactive restructuring ensues. Initially, bacteremia develops before the formation of specific local lesions, eliciting systemic immune responses during the latent period of microbiosis. This period is marked by hyperplasia of macrophage and plasma cell elements. The interaction of mycobacterial components (proteins and polysaccharides) with the host induces sensitization and immune responses, both humoral (mediated by B-lymphocytes) and cellular (mediated by T-lymphocytes).

During bacterial dissemination in a sensitized host, both paraspecific and specific tuberculosis (TB) changes occur. Paraspecific changes manifest as papules, erythema nodosum, and Ponce syndrome. Morphologically, these changes are characterized by non-specific vasculitis, fibrinoid necrosis, diffuse macrophage and lymphohistiocytic reaction, and nodular macrophage-lymphocytic reaction with granuloma formation. The local TB process may develop with a predominance of allergic or immune tissue reactions, depending on the host's reactive state.

In tissues with heightened sensitivity, necrotic and exudative inflammation occurs, indicative of a delayed-type hypersensitivity (DTH) reaction. The immune tissue response is characterized by productive inflammation, typified by a granulomatous hypersensitivity reaction. The morphological hallmark of this reaction in TB is the formation of specific granulomas composed of lymphocytes, monocytes, and macrophages. The progression of granulomatous hypersensitivity is marked by the transformation of macrophages into epithelioid cells (key markers of granulomas), which subsequently form Langhans giant cells.

Effector lymphocytes, particularly activated T lymphocytes, play a crucial role in granulomatous hypersensitivity reactions by producing lymphokines that

promote granuloma formation and enhance the phagocytic and enzymatic functions of macrophages. This activity facilitates the destruction and elimination of Mycobacterium tuberculosis from the host.

The morphological basis of DTH reactions involves a vascular-exudative response, characterized by the activation of B lymphocytes, their differentiation into plasma cells, and the accumulation of antibodies against TB antigens. These antigen-antibody complexes exert a toxic effect on tissues. Mixed tissue reactions may also occur, displaying features of both granulomatous hypersensitivity and DTH reactions.

TB is characterized by the alternating phases of exudative reactions, which align with clinical exacerbations, and productive granulomatous reactions, which correspond to enhanced immunity and attenuation of the TB process. This dynamic interplay results in a polymorphic morphological picture and accounts for the diverse clinical presentations of TB.

The morphological expression of primary tuberculosis is the primary tuberculosis complex, which includes:

1) **Primary Focus**: The initial lesion site in the organ where the pathogens have penetrated.

2) **Lymphangitis**: Specific inflammation of the lymphatic vessels, through which tuberculosis bacteria spread from the primary focus to regional lymph nodes.

3) **Lymphadenitis**: Inflammation of the lymph nodes with characteristic tuberculous changes.

The primary focus is most commonly located in the lungs, less frequently in the ileum, and very rarely in other organs. In the lungs, the focus typically forms subpleurally, often in the III, VIII, IX, and X segments, with a higher incidence in the right lung. Initially, the primary focus presents as exudative pneumonia, with the exudate quickly undergoing caseous necrosis, around which a zone of peripheral serous inflammation develops.

As immune responses strengthen and the exudative process wanes, peripheral inflammation is resorbed. Macrophages accumulate around the periphery of the necrosis and transform into epithelioid cells, with T- and B-lymphocytes also aggregating in this area. The fusion of epithelioid cells forms Langhans giant cells. Epithelioid-cell nodules develop in the peripheral areas of specific granulation tissue, and fibroblasts appear, forming a capsule around the lesion. This capsule lacks blood and lymphatic vessels.

The potential courses of primary tuberculosis are:

1) **Resolution of Primary Tuberculosis** and Healing of Primary Complex Lesions:

a) **Encapsulation**, **Calcification**, and **Ossification** of the Primary Lung Lesion: This results in the formation of a Ghon focus.

b) **Fibrosis** of Tuberculosis Nodules: At the site of tuberculosis lymphangitis, leading to a fibrous scar.

c) **Petrification** and **Ossification** of Affected Lymph Nodes.

d) **Scar Formation** at the Site of Tuberculosis Ulcer: In the intestine.

2) **Progression of Primary Tuberculosis** with Generalized Spread of the Disease, presenting in four forms:

a) **Hematogenous Progression**: Occurs when mycobacteria enter the bloodstream, presenting in two forms:

Miliary Tuberculosis: Characterized by the appearance of multiple small nodules (millet seed-sized) in various organs.

Large-Nodule Tuberculosis: Involves the formation of larger lesions throughout the body.

b) **Lymphogenous Progression**: Involves the spread of the tuberculosis process to new lymph node groups beyond the regional ones. In the case of the pulmonary complex, this can include the peritracheal, supraclavicular, subclavian, and cervical lymph nodes. For the intestinal complex, it can involve all mesenteric lymph node groups, leading to tuberculous mesenteric adenitis.

c) **Growth of the Primary Lesion**: The most severe form of progression, characterized by extensive caseous necrosis of the perifocal inflammation zone. This can lead to the development of lobar caseous pneumonia (rapidly progressive tuberculosis), which can be fatal.

d) **Mixed Form of Spread**: Observed in weakened patients, combining elements of both hematogenous and lymphogenous dissemination.

3) Chronic Course (**Chronic Primary Tuberculosis**) can occur in two scenarios:

a) **Progression from Healed Primary Lesion in the Lymph Nodes**: The disease progresses with the involvement of new lymph node groups, leading to a chronic course with alternating relapses and remissions. This results in a mixture of old changes (petrifications) with fresh caseous lymphadenitis in the lymph nodes.

b) **Formation of a Primary Lung Cavity**: This leads to the development of primary pulmonary tuberculosis, characterized by the formation of a cavitary lesion in the lung.

These courses illustrate the diverse and complex nature of tuberculosis progression, which can vary significantly depending on the host's immune response and the pathways of mycobacterial dissemination.

Hematogenous tuberculosis occurs following a primary tuberculosis infection, particularly in the presence of hematogenous seeding foci or incompletely healed foci in lymph nodes. This occurs against a backdrop of pronounced immunity to mycobacteria but increased sensitivity (sensitization) to tuberculin. In this condition, a productive tissue reaction, primarily granuloma formation, predominates, and there is a significant tendency toward hematogenous dissemination.

The varieties of hematogenous tuberculosis are:

1) **Generalized Hematogenous Tuberculosis**: The most severe form, characterized by uniform eruptions of tuberculosis nodules in multiple organs, and is represented by:

a) **Acute Tuberculosis Sepsis**: A rapidly progressive and fatal form.

b) **Acute Generalized Miliary Tuberculosis**: Characterized by the widespread distribution of small, millet seed-sized nodules in various organs.

c) **Acute Generalized Massive Tuberculosis**: Involves the formation of larger lesions throughout multiple organs.

d) **Chronic Generalized Miliary Tuberculosis**: Often with predominant localization in the lungs, characterized by persistent, widespread, small nodular lesions.

2) **Hematogenous Tuberculosis with Predominant Lung Involvement** can be classified into:

a) **Acute Miliary Tuberculosis**: Characterized by the formation of numerous small nodules (miliary nodules) throughout both lungs, typically concentrated in the upper segments. This form can be either productive, with granuloma formation, or exudative, involving more inflammatory and fluid components.

b) **Chronic Miliary Tuberculosis**: Involves the scarring of miliary nodules, leading to emphysema of the lungs and hypertrophy of the right ventricle of the heart (cor pulmonale).

c) **Chronic Massive or Hematogenously Disseminated Tuberculosis**: This form affects the upper lung segments, especially the cortico-pleural and dorsal sections of the lobes. The nodules are located in the interstitial tissue and inter-alveolar septa and quickly undergo organization, leading to a small mesh-like pattern of fibrosis followed by diffuse emphysema.

The most common form of hematogenous tuberculosis is acute miliary tuberculosis, which can present as either productive or exudative and manifests with the formation of multiple nodules primarily in both lungs.

A unique form of hematogenous tuberculosis in adults is chronic massive tuberculosis, characterized by the involvement of the upper lung segments, particularly the cortico-pleural and dorsal sections of the lobes. Nodules located in the interstitial tissue and inter-alveolar septa quickly organize, resulting in a small mesh-like fibrosis and subsequent diffuse emphysema.

3) **Hematogenous Tuberculosis with Predominantly Extrapulmonary Lesions**: Arises from hematogenous seeding foci, representing secondary dissemination of primary tuberculosis. This form can involve various organs outside the lungs, such as the lymph nodes, bones, kidneys, and central nervous system, reflecting the widespread dissemination of the infection through the bloodstream.

The manifestations of extrapulmonary tuberculosis are diverse, particularly affecting children's bones. The rapidly growing, well-vascularized vertebral bodies, epiphyses, metaphyses of long bones, and pelvic bones are commonly involved. Osteomyelitis can develop in two distinct forms:

1) **Acute Caseous Osteomyelitis**: Characterized by large-cavitary disease with sequestra, marked by extensive tissue destruction without the formation of bony bumps.

2) **Chronic Granulomatous Osteomyelitis**: A slowly progressive condition where granulation tissue, often resembling fibrous osteodystrophy, predominates and lacks the characteristic signs of acute inflammation.

Inflammation often extends beneath the spinal ligamentous apparatus, typically descending along the intermuscular connective tissue. This can form "running abscesses" (sinuses) in the groin region. The walls of these abscesses consist of gradually scarred specific granulation tissue. The process may also extend upward, where the sinuses can compress the trachea, aorta, and esophagus. If the inflammation spreads posteriorly into the spinal canal, it may damage the spinal cord's sheaths. Destruction of multiple adjacent vertebrae can lead to kyphotic deformity of the spine.

Tuberculosis of the joints, such as coxitis (hip joint) and gonitis (knee joint), occurs due to the spread of the inflammatory process from a primary focus in the epiphysis to the synovial membrane. This can manifest either as:

1) **Exudative Inflammation**: Characterized by the accumulation of inflammatory fluid within the joint.

2) **Granulomatous Arthritis**: Involving the formation of granulomas within the joint tissue.

Tuberculosis of the kidneys typically originates from metastatic foci in the cortical layer. Clinical symptoms become evident only after the inflammatory process extends to the pyramids and calyces of the kidneys. Without specific treatment, the infection can spread further, affecting the ureters, urinary bladder, and potentially ascending to the other kidney. Kidney tuberculosis can present in various forms, including:

1) **Focal Caseous-Necrotic**: Involving localized areas of tissue necrosis.

2) **Cavernous**: Characterized by the formation of cavities within the kidney.

3) **Fibrous-Cavernous**: Where fibrous tissue forms around the cavities, leading to structural changes in the kidney.

In deceased individuals with tuberculosis, secondary tuberculosis is most commonly detected. This results from either exogenous reinfection or exacerbation of a previously existing process in the area of the primary complex or extrapulmonary foci. The latter is possible only if the pathogens, even with weakened virulence, remain in these areas.

Characteristic features of secondary tuberculosis include:

1) **Selective Pulmonary Localization**: The process primarily affects the lungs.

2) **Contact and Intracanalicular Spread**: The disease spreads through direct contact and along the bronchial tree or gastrointestinal tract.

3) **Changes in Clinical-Morphological Forms**: These represent different phases of the tuberculosis process in the lungs, reflecting the disease's progression and variability in presentation.

Forms of secondary tuberculosis:

1. Acute focal.
2. Fibrous-focal.

3. Infiltrative.
4. Tuberculoma.
5. Caseous pneumonia.
6. Acute cavernous.
7. Fibrous-cavernous.

Acute Focal Tuberculosis

Typically observed in individuals aged 20-25 and above, this form presents as an Abricosov's reinfection focus.

These foci represent the initial manifestations of secondary tuberculosis and involve specific endobronchitis, mesobronchitis, and panbronchitis within the lobar bronchus.

This leads to the development of acinous or lobular caseous pneumonia, surrounded by a wall of epithelioid cells and giant Langhans cells.

Additionally, a nonspecific reactive inflammatory process develops in the lung roots. In most cases, the process resolves spontaneously, with the caseous necrosis foci becoming encapsulated and undergoing petrification.

Fibrous-Focal Tuberculosis

This represents a phase of acute focal tuberculosis where, after a period of disease remission, the process reactivates. The source of exacerbation is Ashoff-Pulevsky foci, around which acinous and lobular foci of caseous pneumonia arise, subsequently becoming encapsulated and petrified. Alongside Ashoff-Pulevsky foci, ossified and calcified Simon foci may occur due to hematogenous seeding during the primary infection period. In this scenario, the tendency toward exacerbation persists.

Infiltrative Tuberculosis

In this form, changes occur around caseous foci, and the process extends beyond the lobe and even segment of the lung. Perifocal inflammation predominates over caseous changes, which may be minimal. This focus is referred to as the Assman-Redeker focus.

Tuberculoma

This form of secondary tuberculosis emerges as a unique phase of the evolution of infiltrative tuberculosis. In tuberculoma, the perifocal inflammation is resorbed, leaving behind a focus of caseous necrosis surrounded by a capsule. Radiographically, tuberculomas often resemble peripheral lung cancer due to their well-defined borders.

Caseous pneumonia

Typically observed during the progression of infiltrative tuberculosis, caseous pneumonia occurs as the caseous changes begin to predominate over perifocal changes. This can result in the formation of acaseous, lobular, or segmental caseous-pneumonic focus, which, when merged, can occupy large areas of the lung, up to the

entire lobe. Caseous pneumonia is commonly seen in the terminal stage of any form of tuberculosis (except tuberculoma) or in immunocompromised individuals. In caseous pneumonia, the affected lung appears enlarged, dense, and yellow upon sectioning, with fibrinous deposits on the pleura.

Acute cavernous tuberculosis

This form of secondary tuberculosis is characterized by the rapid formation of a cavity or multiple cavities within the site of an infiltrate or tuberculoma.

These caverns typically localize in 1-2 segments of the lung, exhibiting an oval or round shape and communicating with the lumen of a segmental bronchus.

The cavern's wall presents heterogeneity: its inner layer comprises caseous masses, while the outer layer consists of lung tissue that has become condensed due to inflammation.

Fibrocavernous tuberculosis

Arising from acute cavernous tuberculosis, this form occurs when the disease becomes chronic.

The cavern's wall is dense and features three layers: an inner (pyogenic) necrotic layer, a middle layer of tuberculous granulation tissue, and an outer layer of connective tissue.

Within these layers, patches of lung atelectasis may be visible. Tuberculous granulation tissue gradually matures into scar tissue surrounding the cavity, which can form at any stage of the disease. As scar tissue proliferates, it leads to significant growths in the surrounding lung tissue.

Consequently, the affected organ undergoes shrinkage, and the pleura may thicken sharply, sometimes contributing to the cavern's walls.

In addition to cavities surrounded by connective tissue growth, fibrocavernous tuberculosis may also exhibit numerous bronchiectases in the lungs.

Complications of tuberculosis

In primary tuberculosis, pleurisy can occur, characterized by a significant presence of leukocytes in the exudate.

Bone tuberculosis typically presents with sequestrum formation, deformities, abscesses, and fistulae.

In secondary tuberculosis, complications often arise from cavitation, including bleeding, pneumothorax, and empyema of the pleura, especially when a cavity ruptures into the pleural cavity.

In any form, particularly in fibrocavitary tuberculosis, the prolonged course of the disease can lead to amyloidosis, specifically AA amyloidosis.

Chronic tuberculosis commonly results in the development of pulmonary heart and subsequent pulmonary heart failure.

INFORMATIONAL AND METHODOLOGICAL PART

MAIN LITERATURE

1. Pathomorphology : textbook / ed. by I.V. Sorokina, V.D. Markovskyi, D.I. Halata. - 2nd ed. - Kyiv : AUS Medicine Publishing, 2020. - 327 p., [10] col. inserts : tab.

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.