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: viral infections”

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 study the definition, classification, etiology, pathogenesis, morphology, clinical presentation, complications, and outcomes of viral infections. To analyze viral hepatitis: hepatitis A (HAV – fecal-oral, self-limited, no chronicity), hepatitis B (HBV – parenteral, sexual, perinatal; acute and chronic hepatitis, cirrhosis, hepatocellular carcinoma; ground-glass hepatocytes on histology), hepatitis C (HCV – parenteral, high rate of chronicity, cirrhosis, HCC), hepatitis D (HDV – requires HBV coinfection, superinfection can cause severe acute hepatitis), hepatitis E (HEV – fecal-oral, high mortality in pregnancy). To examine viral hemorrhagic fevers: Ebola, Marburg, Lassa, Dengue, Yellow fever. To analyze herpesvirus infections: herpes simplex virus (HSV-1, HSV-2 – vesicular lesions, mucocutaneous, encephalitis, neonatal herpes – Cowdry type A inclusions), varicella-zoster virus (VZV – chickenpox, shingles), Epstein-Barr virus (EBV – infectious mononucleosis, nasopharyngeal carcinoma, Burkitt lymphoma, post-transplant lymphoproliferative disorder – atypical lymphocytes (Downey cells), Reed-Sternberg-like cells), cytomegalovirus (CMV – opportunistic infection in immunocompromised – owl's eye inclusions in enlarged cells, pneumonitis, retinitis, colitis, encephalitis), human herpesvirus 8 (HHV-8 – Kaposi sarcoma). To analyze respiratory viral infections: influenza virus (seasonal epidemics, pandemics – tracheitis, bronchitis, pneumonia, diffuse alveolar damage), respiratory syncytial virus (RSV – bronchiolitis in infants, syncytial giant cells), adenovirus (pharyngitis, conjunctivitis, pneumonia, inclusion bodies). To examine human immunodeficiency virus (HIV): pathogenesis (CD4+ T cell depletion), stages (acute retroviral syndrome, clinical latency, AIDS), opportunistic infections (Pneumocystis jirovecii pneumonia, toxoplasmosis, CMV, mycobacteria), neoplasms (Kaposi sarcoma, non-Hodgkin lymphoma, cervical carcinoma), HIV-associated nephropathy (HIVAN – collapsing FSGS). To describe morphological features of viral infections: cytopathic effects (inclusion bodies – intranuclear: Cowdry type A in HSV/VZV/CMV/adenovirus; intracytoplasmic: Negri bodies in rabies, Molluscum bodies; ground-glass nuclei in HBV), syncytia formation (RSV, HIV), ballooning degeneration (viral hepatitis), lymphocytic infiltration.

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 classification and morphology of viral hepatitis (A, B, C, D, E);
- The morphological features of herpesvirus infections (HSV, VZV, EBV, CMV) including inclusion bodies;
- The pathogenesis and morphology of HIV/AIDS and associated opportunistic infections;
- The cytopathic effects of viruses (inclusion bodies, syncytia, ballooning degeneration);
- The complications and outcomes of viral infections.

Be able to:

- Identify ground-glass hepatocytes in chronic hepatitis B;
- Recognize Cowdry type A inclusions in HSV and CMV;
- Identify owl's eye inclusions in CMV;
- 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:

Viral infections are among the most common causes of human disease worldwide, ranging from self-limited illnesses to chronic debilitating conditions and fatal diseases. Viral hepatitis affects hundreds of millions of people and is a leading cause of cirrhosis and liver cancer. Herpesviruses cause lifelong latent infections with potential for reactivation. HIV/AIDS remains a global pandemic with significant morbidity and mortality. Understanding the morphological features of viral infections is essential for infectious disease specialists, pathologists, internists, pediatricians, and public health professionals for diagnosis, treatment, and prevention.

QUESTIONS

1. Influenza. Definition. Etiology. Morphology of community-acquired viral pneumonias (CAVP). Complications and outcomes.
2. SARS-CoV-2. Definition. Etiology. Morphology of community-acquired viral pneumonias (CAVP). Complications and outcomes.

3. Parainfluenza. Definition. Etiology. Morphology of community-acquired viral pneumonias (CAVP). Complications and outcomes.

4. Adenoviral infection. Definition. Etiology. Morphology of community-acquired viral pneumonias (CAVP). Complications and outcomes.

5. RSV-infection. Definition. Etiology. Morphology of community-acquired viral pneumonias (CAVP). Complications and outcomes.

6. CMV-infection. Definition. Etiology. Complications and outcomes.

7. HIV-infection. Definition. Etiology. Pathogenesis. Morphology of different stages of the disease. The concept of opportunistic infections. AIDS. Causes of death.

COURSE OF THE SESSION

Community-acquired viral pneumonias (**CAVP**) encompass a range of respiratory infections caused by viruses commonly found within communities. Among the most prevalent culprits are **influenza virus types A and B, respiratory syncytial viruses, human metapneumovirus, adenovirus, rhinoviruses, rubeola,** and **varicella viruse**s. These viruses typically initiate as mild upper respiratory tract infections akin to the common cold but can escalate into more severe lower respiratory tract infections.

Several **factors contribute to the progression of viral infections** to pneumonia. Individuals at the extremes of age, those suffering from malnutrition, alcoholism, or underlying debilitating illnesses are particularly susceptible. Once the viruses breach the respiratory lining, they exploit specific cellular receptors to gain entry and replicate within respiratory epithelial cells. This replication process triggers **cytopathic changes**, leading to **cell death** and **subsequent inflammation**.

Viral replication and inflammation damage the respiratory epithelial cells and **impair mucociliary clearance mechanisms**. When this process is compromised, mucus and debris may accumulate, providing an ideal environment for bacteria to thrive and colonize.

As a result, the weakened lung defenses create an opportunity for bacteria to establish **secondary infections**. These bacterial superinfections often manifest with **more severe symptoms** and can lead to complications such as bacterial pneumonia or respiratory failure. In some cases, these secondary bacterial infections pose greater risks to the individual's health than the initial viral pneumonia itself.

In essence, the impaired mucociliary clearance and damaged lung tissue caused by the viral infection create an environment conducive to bacterial growth, leading to increased severity and complications of the respiratory illness.

Clinical manifestations of CAVP

1. **Fever**: Elevated body temperature is a hallmark symptom of viral pneumonia and may range from mild to high-grade fevers.
2. **Cough**: Persistent cough, often productive of clear or mucoid sputum, is a common symptom of CAVP. The cough may be dry or become productive as the infection progresses.
3. **Shortness of breath**: Dyspnea or difficulty breathing can occur, particularly in more severe cases or in individuals with underlying respiratory conditions.
4. **Chest pain**: Chest discomfort or pain, typically described as sharp or pleuritic in nature, may be present due to inflammation of the lung tissue.
5. **Fatigue**: Generalized weakness and fatigue are common symptoms accompanying viral pneumonia, reflecting the body's immune response and the energy expended in fighting the infection.
6. **Muscle aches**: Myalgias, or muscle aches and pains, are frequently reported in individuals with viral pneumonia, contributing to the overall sense of malaise.
7. **Headache**: Some individuals may experience headaches, which can range from mild to severe and may be associated with fever and systemic inflammation.

8. **Sore throat**: Pharyngitis or a sore throat can occur, particularly in the early stages of the infection, resembling symptoms of an upper respiratory tract infection.

9. **Nasal congestion**: Congestion of the nasal passages and sinuses may be present, accompanied by rhinorrhea (runny nose) in some cases.

10. **Gastrointestinal symptoms**: Nausea, vomiting, and diarrhea may occur, albeit less commonly, especially in children or in cases where the viral infection affects multiple organ systems.

11. **Confusion or altered mental status**: In severe cases, particularly in older adults or individuals with underlying neurological conditions, confusion or altered mental status may be observed.

It's important to note that the clinical presentation of CAVP can overlap with other respiratory infections, including bacterial pneumonia and bronchitis.

Influenza

Etiology

Influenza viruses of type A pose a significant threat to human health, capable of infecting various species including humans, pigs, horses, and birds. These viruses are notorious for instigating both pandemic and epidemic influenza outbreaks, rendering them a focal point of public health concern.

Pathogenesis

Central to the virulence of influenza viruses are the hemagglutinin (HA) and neuraminidase (NA) proteins encoded within their genome. Hemagglutinin, existing in subtypes H1, H2, and H3, facilitates viral attachment to host cells, while neuraminidase, with subtypes N1 and N2, aids in the release of viral progeny from infected cells.

Clinical Manifestations

Clinical manifestations of influenza infection typically encompass a spectrum of respiratory symptoms, including fever, cough, sore throat, nasal congestion, and fatigue. Dyspnea or difficulty breathing may ensue, particularly in severe cases. Headache, myalgias, and gastrointestinal symptoms such as nausea and vomiting may also be present, albeit less frequently.

Morphology

The pathological morphology of influenza pneumonia is characterized by diffuse alveolar damage, interstitial inflammation, and alveolar hemorrhage. Microscopically, there may be evidence of epithelial cell necrosis, inflammatory cell infiltration, and hyaline membrane formation. In cases of secondary bacterial pneumonia, additional features such as abscess formation, suppurative inflammation, and necrotizing pneumonia may be observed.

Post-mortem pulmonary gross findings in an influenza A patient. (A) Gross appearance of the lung of a 61-year old female patient showing diffuse haemorrhagic consolidation suggestive of bronchopneumonia, predominantly in the lower lobe (arrows). (B,C) Higher magnification from the same lung reveals open vessels and consolidation (arrows).

Human Metapneumovirus

Etiology

Human metapneumovirus (HMPV) belongs to the paramyxovirus family and was first identified in 2001. It is prevalent worldwide and is known to cause both upper and lower respiratory tract infections. While HMPV infections can occur across all age groups, they are most frequently observed in young children, elderly adults, and individuals with compromised immune systems.

Pathogenesis

HMPV infections can manifest as a spectrum of respiratory illnesses, ranging from mild upper respiratory tract infections to severe lower respiratory tract complications such as bronchiolitis and pneumonia. The pathogenesis of HMPV infections involves viral infiltration of the respiratory epithelium, eliciting an inflammatory response. This response can lead to airway obstruction, impaired gas exchange, and respiratory distress.

Clinical Manifestations

Clinical manifestations of HMPV infections closely resemble those caused by human respiratory syncytial virus (RSV) and are often mistaken for influenza. Common symptoms include fever, cough, wheezing, nasal congestion, and difficulty breathing. Severe cases may present with respiratory distress, cyanosis, and signs of pneumonia. In children, HMPV is responsible for a significant proportion of hospitalizations and outpatient visits for acute respiratory tract infections.

Morphology

The pathological morphology of HMPV infections typically involves inflammation and damage to the respiratory epithelium. Microscopic examination may reveal epithelial cell necrosis, inflammatory cell infiltration, and formation of syncytia. In severe cases, alveolar damage and consolidation indicative of pneumonia may be observed.

Diagnosis of human metapneumovirus (HMPV) infections predominantly hinges on the utilization of polymerase chain reaction (**PCR**) tests, a highly sensitive molecular technique capable of detecting viral RNA in respiratory specimens. These specimens typically include nasopharyngeal swabs, throat swabs, or respiratory secretions obtained through methods such as bronchoalveolar lavage.

In addition to PCR testing, **serological assays** play a complementary role in diagnosing HMPV infections by detecting antibodies against the virus in serum samples. Serological tests, such as enzyme-linked immunosorbent assays (**ELISA**) or immunofluorescence assays (**IFA**), are valuable tools for assessing an individual's immune response to HMPV exposure. By detecting the presence of specific HMPV antibodies, these tests aid in confirming recent or past infections, determining the **seroprevalence of HMPV in populations**, and assessing the efficacy of potential vaccines.

Human Coronaviruses

Etiology

Coronaviruses constitute a family of enveloped, positive-sense RNA viruses that infect humans and various other vertebrate species. Within this family, weakly pathogenic coronaviruses typically cause mild upper respiratory tract infections

resembling the common cold. In contrast, highly pathogenic coronaviruses can induce severe and often fatal pneumonia, posing significant public health threats.

Pathogenesis

Highly pathogenic coronaviruses, exemplified by SARS-CoV-2, exhibit a particular affinity for the lung due to their binding to the angiotensin-converting enzyme 2 (ACE2) protein present on the surface of pulmonary alveolar epithelial cells. Upon infection, susceptible hosts, particularly older individuals with underlying medical conditions, may mount an intense immune response characterized by the release of pro-inflammatory cytokines. This immune dysregulation, coupled with direct viral damage to lung tissue, can precipitate acute lung injury and progression to acute respiratory distress syndrome (ARDS), contributing to the severity of the disease.

Clinical Manifestations

Clinical manifestations of highly pathogenic coronaviruses, such as SARS-CoV-2, encompass a broad spectrum of respiratory symptoms. Common symptoms include fever, cough, dyspnea, and fatigue. Some individuals may also experience anosmia (loss of smell) or dysgeusia (altered sense of taste). Severe cases may progress rapidly to respiratory failure and multiorgan dysfunction, particularly in vulnerable populations with pre-existing comorbidities.

Morphology

The pathological morphology of highly pathogenic coronavirus infections typically involves diffuse alveolar damage, interstitial inflammation, and hyaline membrane formation. Microscopically, there may be evidence of extensive epithelial cell necrosis, inflammatory cell infiltration, and fibrin deposition within the alveolar spaces. In severe cases, organizing pneumonia and fibrosis may develop as part of the reparative process, contributing to long-term respiratory sequelae in survivors.

Morphology of CAVP

Viral respiratory infections elicit characteristic morphologic changes across various anatomical regions of the respiratory tract.

In upper respiratory infections, conspicuous features include **mucosal hyperemia and swelling**, alongside infiltration of the submucosa by mononuclear cells, primarily lymphocytes and monocytes.

Additionally, there is an **excess production of mucus secretions**, which can obstruct nasal channels, sinuses, or the Eustachian tubes, predisposing individuals to secondary bacterial infections.

Notably, virus-induced tonsillitis frequently induces **hyperplasia of lymphoid tissue** within the Waldeyer ring, particularly prevalent in pediatric populations.

In cases of viral **laryngotracheobronchitis** and **bronchiolitis**, vocal cord swelling and copious mucus production are hallmark findings.

Impairment of bronchociliary function exacerbates susceptibility to bacterial superinfection, often characterized by more pronounced suppuration.

The obstruction of small airways can lead to focal **lung atelectasis**, while severe bronchiolar involvement may result in widespread plugging of secondary and terminal airways by cell debris, fibrin, and inflammatory exudate.

Prolonged obstruction may culminate in the **organization** and **fibrosis** typical of **obliterative bronchiolitis**, contributing to permanent lung damage.

Lung involvement in viral pneumonias can vary in distribution, **from patchy to diffuse**, potentially affecting entire lobes bilaterally or unilaterally.

Affected areas typically exhibit red-blue congestion, with infrequent occurrences of **pleuritis** or pleural effusions.

Histologically, the prevailing pattern is an **interstitial inflammatory reaction** involving the walls of the alveoli.

Alveolar septa demonstrate widening and edema, often containing a **mononuclear inflammatory infiltrate** comprised of lymphocytes, macrophages, and occasionally plasma cells.

In severe cases, **neutrophils may also be present**, alongside intra-alveolar proteinaceous material and cellular exudate.

Complications such as acute respiratory distress syndrome (**ARDS**) may manifest with the formation of **pink hyaline membranes lining the alveolar walls**.

Resolution of the infection typically involves the **reconstitution of normal lung architecture**, although superimposed bacterial infections can modify the histologic picture, resulting in ulcerative bronchitis, bronchiolitis, and bacterial pneumonia.

Certain viruses, including herpes simplex, varicella, and adenovirus, may be associated with **necrosis of bronchial and alveolar epithelium**, precipitating acute inflammation and exacerbating the pathologic sequelae of viral respiratory infections.

CMV infection

Etiology

Cytomegalovirus (CMV) infection is caused by the cytomegalovirus, a member of the Herpesviridae family. It is a ubiquitous virus that can infect humans of all ages and may remain latent within the host for life, periodically reactivating under certain conditions.

Pathogenesis

Upon initial infection, CMV targets epithelial cells at mucosal surfaces, gaining entry via mucosal membranes or breaks in the skin. The virus then disseminates via the bloodstream to various organs, including the lungs, colon, and cervix, where it establishes latent infection within specific cell types, particularly endothelial cells and monocytes. In immunocompetent individuals, the immune system effectively controls viral replication, leading to asymptomatic or mild symptomatic infections. However, in immunocompromised individuals, such as those with HIV/AIDS or undergoing immunosuppressive therapy, CMV can cause severe disease due to uncontrolled viral replication and dissemination.

Clinical manifestations of CMV infection vary depending on the individual's immune status. Immunocompetent individuals may experience mild symptoms or

remain asymptomatic. However, in immunocompromised individuals, CMV infection can manifest as a systemic illness with fever, malaise, and lymphadenopathy. In severe cases, CMV can cause organ-specific manifestations, including pneumonia in the lungs, colitis in the colon, and cervicitis in the cervix. These manifestations can lead to significant morbidity and mortality, particularly in immunocompromised patients.

Morphology

In the lungs, CMV infection can result in interstitial pneumonia characterized by diffuse alveolar damage, intra-alveolar hemorrhage, and the presence of cytomegalic cells with characteristic "owl's eye" intranuclear inclusions within alveolar epithelial cells. In the colon, CMV infection can cause ulcerative colitis with deep ulcerations, inflammation, and the presence of cytomegalic cells within the mucosa and submucosa. In the cervix, CMV infection may lead to cervicitis characterized by inflammation, ulceration, and the presence of cytomegalic cells within cervical epithelial cells.

Human Immunodeficiency Virus (HIV) infection is a chronic, progressive, retroviral disease characterized by persistent viral replication, progressive destruction of CD4+ T lymphocytes, profound immunosuppression, and subsequent susceptibility to a spectrum of opportunistic infections and malignancies. The terminal phase of this disease continuum is designated the acquired immunodeficiency syndrome (AIDS), a condition defined by specific clinical and immunological criteria, including a CD4+ T-cell count below 200 cells/μL or the presence of an AIDS-defining illness.

Etiology

The etiological agent is HIV, a cytopathic lentivirus belonging to the family Retroviridae. Two major types are recognized: HIV-1, which is responsible for the global pandemic, and HIV-2, which is less virulent and primarily confined to West Africa. The viral structure comprises a conical capsid core enclosing two copies of single-stranded positive-sense RNA and the viral enzymes reverse transcriptase, integrase, and protease. A lipid envelope derived from the host cell membrane is studded with the surface glycoprotein gp120 (responsible for CD4 receptor and co-receptor binding) and the transmembrane glycoprotein gp41 (mediating membrane fusion). Genetic variability, particularly within the *env* gene, is a hallmark of HIV and underlies immune evasion and antiretroviral drug resistance.

Pathogenesis

The pathogenesis of HIV infection is a dynamic interplay between viral replication and host immune responses. The primary pathogenic event is the selective tropism of HIV for cells expressing the CD4 surface molecule, most notably CD4+ T helper lymphocytes, as well as macrophages and dendritic cells. Following mucosal or parenteral inoculation, HIV binds to the CD4 receptor via gp120, initiating a conformational change that permits subsequent interaction with a chemokine co-receptor, either CCR5 (predominant in early, macrophage-tropic strains) or CXCR4 (associated with later, T-cell-tropic strains). This engagement facilitates gp41-mediated fusion and viral entry.

Upon entry, reverse transcriptase converts the viral RNA into double-stranded proviral DNA, which is then integrated into the host genome by integrase. The integrated provirus may remain transcriptionally latent or direct the production of new virions via the host transcriptional machinery, culminating in budding and release (aided by protease-mediated cleavage of precursor polyproteins). Chronic viral replication leads to a relentless loss of CD4+ lymphocytes through multiple mechanisms: direct cytopathic effect from viral budding, syncytia formation (fusion of infected and uninfected CD4+ cells), activation-induced apoptosis, and elimination by cytotoxic T lymphocytes (CTLs) targeting infected cells. Despite robust humoral and cellular immune responses, the virus evades eradication due to its high mutation rate, establishment of latent reservoirs in resting memory CD4+ T cells, and downregulation of major histocompatibility complex (MHC) class I molecules on infected cells. The net result is progressive immunosenescence, immune dysregulation, and a quantitative and qualitative defect in cell-mediated immunity.

Morphology of Different Stages of the Disease

The morphological findings in HIV infection vary according to the stage of disease, ranging from reactive lymphoid hyperplasia in early stages to severe lymphoid depletion and opportunistic pathology in AIDS.

Primary (Acute) Stage: Histopathological examination of lymph nodes during the first weeks after seroconversion reveals florid follicular hyperplasia. The germinal centers are enlarged, irregular, and contain abundant proliferating B cells, accompanied by numerous tingible-body macrophages. A characteristic feature is the presence of follicular dendritic cell (FDC) networks heavily coated with HIV virions trapped within immune complexes. The paracortical T-cell zone shows some CD4+ T-cell depletion, though the architecture is largely preserved.

Chronic (Latent) Stage: Over months to years, the lymph nodes evolve from follicular hyperplasia to a pattern of *follicular involution* or *follicular lysis*. Germinal centers become disrupted, fragmented, and depleted of FDCs. There is progressive paracortical expansion of CD8+ T cells, partially compensating for the declining CD4+ population. The splenic white pulp similarly shows atrophy of germinal centers and periarteriolar lymphoid sheaths. These changes coexist with ongoing viral replication and low-grade inflammation.

AIDS Stage: The end-stage lymphoid tissue demonstrates profound *lymphoid depletion* or *burned-out* appearance. Lymph nodes are small, hypocellular, and largely replaced by fibrotic tissue. Remaining germinal centers are absent or vestigial. The spleen, thymus (showing marked involution and loss of Hassall's corpuscles), and gut-associated lymphoid tissue (GALT) exhibit similar atrophic changes. This anatomic correlate of severe immunosuppression sets the stage for the development of opportunistic infections and neoplasms.

The Concept of Opportunistic Infections

Opportunistic infections are infections caused by pathogens that are typically of low virulence or are commensal organisms in an immunocompetent host, but

which cause severe, disseminated, or atypical disease in the setting of compromised immunity. In HIV-infected individuals, the precise pattern of opportunistic infections correlates with the degree of CD4+ T-cell decline.

- **CD4+ count > 500 cells/μL:** Oral or vaginal candidiasis, fungal skin infections, herpes zoster.
- **CD4+ count 200–500 cells/μL:** Pulmonary tuberculosis (reactivation), bacterial pneumonia, herpes simplex virus ulcers, Kaposi sarcoma (due to human herpesvirus-8).
- **CD4+ count < 200 cells/μL (AIDS threshold):** *Pneumocystis jirovecii* pneumonia (PJP), disseminated *Mycobacterium avium* complex (MAC), progressive multifocal leukoencephalopathy (JC virus), toxoplasmosis (reactivation of *Toxoplasma gondii* cysts in brain), cryptococcal meningitis.
- **CD4+ count < 50 cells/μL:** Disseminated cytomegalovirus (CMV) retinitis, colitis, or encephalitis; disseminated *Mycobacterium tuberculosis* (in high-prevalence regions); primary central nervous system lymphoma (Epstein-Barr virus driven).

Morphologically, these infections often lack the characteristic inflammatory response (e.g., minimal neutrophil or granulomatous reaction) due to the inability to mount an effective immune response. For instance, in PJP, the alveoli are filled with foamy, eosinophilic acellular exudate comprising cysts of *Pneumocystis jirovecii*, with little to no lymphocytic or neutrophilic infiltrate.

AIDS: Definition and Diagnostic Criteria

According to the Centers for Disease Control and Prevention (CDC) revised classification system (1993), AIDS is diagnosed in any HIV-infected individual who meets one of the following criteria:

1. A CD4+ T-lymphocyte count less than 200 cells/μL (or a CD4+ percentage less than 14%).
2. The presence of one or more AIDS-defining conditions, regardless of CD4+ count. These conditions include, but are not limited to: Candidiasis of esophagus, bronchi, trachea, or lungs; invasive cervical cancer; coccidioidomycosis, disseminated; cryptococcosis, extrapulmonary; cryptosporidiosis, chronic intestinal; CMV retinitis or disseminated disease; HIV-related encephalopathy; herpes simplex with chronic ulcer(s); histoplasmosis, disseminated; Kaposi sarcoma; lymphoma (Burkitt, immunoblastic, or primary brain); MAC or *M. kansasii*, disseminated; *Pneumocystis jirovecii* pneumonia; progressive multifocal leukoencephalopathy; recurrent Salmonella septicemia; toxoplasmosis of brain; and wasting syndrome attributed to HIV.

Causes of Death in HIV-Infected Patients

In the era of effective antiretroviral therapy (ART), the causes of death have shifted dramatically. However, without treatment, the leading causes of death are complications of opportunistic infections and malignancies.

In the pre-ART or untreated setting:

1. **Opportunistic infections** account for approximately 70–80% of deaths. The most common terminal events include *Pneumocystis jirovecii* pneumonia (respiratory failure, often with bilateral alveolar damage), disseminated *Mycobacterium avium* complex (wasting, sepsis, multiorgan failure), cryptococcal meningitis (raised intracranial pressure, cerebral herniation), and CMV pneumonitis or encephalitis.
2. **AIDS-defining malignancies** contribute to 15–20% of deaths, most frequently Kaposi sarcoma (disseminated visceral involvement with pulmonary or gastrointestinal hemorrhage), primary central nervous system lymphoma, and high-grade B-cell non-Hodgkin lymphoma.
3. **HIV-associated wasting syndrome** (involuntary loss >10% of body weight with chronic diarrhea, fever, and weakness) leads to cachexia and metabolic derangements, often as a contributing cause.
4. **Progressive multifocal leukoencephalopathy** (PML) results in relentlessly progressive neurological decline, aspiration pneumonia, and death within months of diagnosis.

In the ART era (current mortality patterns):

1. While opportunistic infections have declined markedly, they still occur in patients with late diagnosis or poor adherence to therapy.
2. **Non-AIDS defining causes** now predominate: accelerated cardiovascular disease (due to chronic inflammation and metabolic effects of ART), chronic liver disease (from co-infection with hepatitis B or C, or ART-associated hepatotoxicity), chronic kidney disease (HIV-associated nephropathy or ART toxicity), non-AIDS malignancies (lung cancer, anal cancer, Hodgkin lymphoma), and complications of aging (e.g., frailty, neurocognitive decline).
3. **Immune reconstitution inflammatory syndrome (IRIS)** can be a cause of morbidity and mortality when ART is initiated in severely immunocompromised patients, leading to paradoxical exacerbation of subclinical opportunistic infections (e.g., cryptococcal meningitis, tuberculosis) due to sudden restoration of pathogen-specific immune responses.

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.

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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.

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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

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