ZAPOROZHZHIAN STATE MEDICAL UNIVERSITY
The department of pathological anatomy and forensic medicine

Acquired Immunodeficiency Syndrome (AIDS)

Human immunodeficiency virus (HIV)

Lecture on pathological anatomy for the 5th year students

Human immunodeficiency virus (HIV)

HIV is a retrovirus of the lentivirus family. The variant of HIV that is the cause for almost all infections is known as HIV-1.

HIV-2 is much less common and less virulent, but eventually produces clinical findings similar to HIV-1 The HIV-1 type itself has a number of subtypes (A through H and O).

Retroviruses are unable to replicate outside of living host cells because they contain only RNA and do not contain DNA.

The result of HIV infection is relentless destruction of the immune system.

All HIV infected persons are at risk for illness and death from opportunistic infectious and neoplastic complications as a result of the AIDS manifestations

HIV Structure

env include-

the envelope glycoproteins, the outer envelope glycoprotein gp120

transmembrane glycoprotein gp41 derived from glycoprotein precursor gp160.

the **gag** gene include –

core nucleocapsid proteins p55, p40, p24 (capsid, or "core" antigen), p17 (matrix), and p7 (nucleocapsid);

pol are - the enzyme proteins p66 and p51 (reverse transcriptase), p11 (protease), and p32 (integrase)

Pathogenesis. Prevention of Infection

- Major modes of HIV infection spread:

As a sexually transmitted disease. Infection is also aided by the presence of other sexually transmitted diseases that can produce mucosal ulceration and inflammation.

HIV can be spread via blood or blood products, most commonly with shared contaminated needles used by persons engaging in intravenous drug use.

As a perinatal infection. Mothers who are HIV infected can pass the virus on to their fetuses in uterus or to infants via breast milk.

Mechanism of infection

The CD4 receptor is known as a chemokine that is needed for HIV infection. Chemokines are cell surface fusion-mediating molecules. Their presence on cells can aid binding of the HIV envelope glycoprotein gp120, promoting infection. Initial binding of HIV to the CD4 receptor is mediated by conformational changes in the gp120 subunit, but such conformational changes are not sufficient of fusion. The chemokine receptors produce a conformational change in the gp41 subunit which allows fusion of HIV. Over time, mutations in HIV may increase the ability of the virus to infect cells via these routes.

Mechanism of infection

- HIV primarily infects cells with CD4 cell-surface receptor molecule. Many cell types share common epitopes with this protein, though CD4 lymphocytes play a crucial role. In macrophages and in some other cells lacking CD4 receptors, such as fibroblasts, an Fc receptor site or complement receptor site may be used instead for entry of HIV.

Mechanism of infection

- Cells of the mononuclear phagocyte system, principally blood monocytes, T lymphocytes, B lymphocytes, natural killer (NK) lymphocytes, dendritic cells (Langerhans cells of epithelia and follicular dendritic cells in lymph nodes), hematopoietic stem cells, endothelial cells, microglial cells in brain, and gastrointestinal epithelial cells are the primary targets of HIV infection.

- After entering the body, the viral particle is attracted to a cell with the appropriate CD4 receptor molecules where it attaches by fusion to a susceptible cell membrane or by endocytosis and then enters the cell.
- Within the cell, the viral particle un-coats from the envelope to releases its RNA. The enzyme product of the pol gene, reverse transcriptase that is bound to the HIV RNA, provides for reverse transcription of RNA to proviral DNA.

- It is this HIV proviral DNA which is then inserted into host cell genomic DNA by the integrase enzyme. Once the HIV proviral DNA is within the infected cell's genome, it cannot be eliminated or destroyed except by destroying the cell itself.
- The HIV provirus is then replicated by the host cell. The infected cell can then release virions by surface budding, or infected cells can undergo lysis with release of new HIV virions which can then infect additional cells. Antibodies formed against HIV are not protective, and a viremic state can persist despite the presence of even high antibody titers.

After initial entry of HIV and establishment of infection, replication may at first occur within inflammatory cells at the site of infection or within peripheral blood mononuclear cells, but then the major site of replication quickly shifts to lymphoid tissues of the body, including:

- lymph nodes, spleen, liver, and bone marrow,

the gut associated lymphoid tissue.

Primary HIV infection is followed by a burst of viremia in which virus is easily detected in peripheral blood in mononuclear cells and plasma. It is the period of clinical latency of HIV infection, but viral replication actively continues in lymphoid tissues.

The primary target of HIV is the immune system, which is gradually destroyed.

Viral replication actively continues following initial HIV infection, and the rate of CD4 lymphocyte destruction is progressive.

Clinically, HIV infection may appear "latent" for years. During this time, enough of the immune system remains intact to provide immune surveillance and prevent most infections.

When a significant number of CD4 lymphocytes have been destroyed and production of new CD4 cells cannot match destruction, then failure of the immune system leads to the appearance of clinical AIDS.

Onset of AIDS

- Decrease in the total CD4 count below 500/microliter presages the development of clinical AIDS.
- When the CD4 lymphocyte count drops below 200/microliter, then the stage of clinical AIDS has been reached and it is also indicates a high probability for the development of AIDS-related opportunistic infections and/or neoplasms.

Persistent Generalized Lymphadenopathy (PGL)

- There is loss of normal lymph node architecture as the immune system fails with emergence from latency of HIV infection. It is marked by development of generalized lymphadenopathy.
- Lymph nodes throughout the body are large but usually do not exceed 3 cm in size and they may vary in size over time.

Another phase of HIV infection described clinically and is known as AIDS-related complex (ARC), which is not necessarily preceded by PGL.

ARC lacks only the opportunistic infections and neoplasms which define AIDS.

ARC patients usually show symptoms of fatigue, weight loss, and night sweats, along with superficial fungal infections of the mouth and fingernails and toenails (onychomycosis).

It is uncommon for HIV infected persons to die at the stage of

The progression to clinical AIDS is marked by:

1. syncytia-forming (SI) variants of HIV. These SI viral variants, derived from non-syncytia-forming (NSI) variants, have greater CD4 cell tropism and are associated with more rapid CD4+ cell decline. The SI variants typically arise in association with a peripheral blood CD4 lymphocyte count between 400 and 500/microliter, prior to the onset of clinical AIDS
2. by the appearance of the p24 antigen
3. beta2-microglobulin is increased with lymphocyte activation or destruction associated with HIV disease progression.
4. Neopterin is also a measure of immune system activation and can predict HIV disease progression.

Opportunistic infection

Pneumocystis carinii

Cytomegalovirus

Mycobacteria

Fungal Infections

Toxoplasmosis

Herpes simplex

Gastrointestinal Protozoal Infections

Malignant Neoplasms

Miscellaneous

Pneumocystis carinii

It is the most frequent opportunistic infection seen with AIDS. It produces a pulmonary infection, called Pneumocystis carinii pneumonia (PCP).

The most common clinical findings of PCP are: acute onset of fever,

- non-productive cough,
- dyspnea,
- chest radiograph may show perihilar infiltrates.

Cytomegalovirus

- Cytomegalovirus (CMV) is the most frequent disseminated opportunistic infection seen with AIDS.
- It causes the most serious disease:
  as a pneumonia in the lung,
  serious disease in the brain,
  gastrointestinal tract,
  it is a cause for retinitis and blindness at AIDS.
- CMV is identified by the presence of very large cytomegalic cells with enlarged nuclei that contain a violaceous intranuclear inclusion surrounded by a clear halo.

The appearance of Myc. tuberculosis with AIDS is similar to that of non-AIDS patients, with granulomatous pulmonary disease, though the infection may be more extensive or may be disseminated to other organs.

Myc. avium complex (MAC) infection is more unique to AIDS and is characterized by:

involvement mostly of the organs of the mononuclear phagocyte system (lymph node, spleen, liver, marrow);

MAC infections are less likely to produce visible granulomas;

the lesions often consist of clusters of macrophages filled with numerous mycobacteria.

Oral candidiasis is often seen with HIV infection and may presage the progression to AIDS. Candida can occasionally produce invasive infections in esophagus, upper respiratory tract, and lung.

Infections with the pathogenic fungi Cryptococcus neoformans, Histoplasma capsulatum, and Coccidioides immitis are more serious infections that are often widely disseminated. C. neoformans often produces pneumonia and meningitis.

Malignant Neoplasms

1. Kaposi's sarcoma (KS) produces reddish purple patches, plaques, or nodules over the skin and can be diagnosed with skin biopsy. Visceral organ involvement eventually occurs in 3/4 of patients with KS.

2. Malignant lymphomas seen with AIDS are typically of a high grade and extranodal, often in the brain. They are very aggressive and respond poorly to therapy.