Reproductive Team of Pathology

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Systematic manifestation of AIDS

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10th Lecture

AIDS

Acquired immunodeficiency syndrome (AIDS)

HIV-2 is presnt in Africa

Cause: AIDS is the end stage of a disease caused by human immuno-deficiency virus (HIV) infection (so HIV +ve doesn't mean AIDS) and has become a worldwide epidemic since the first clinical description in 1981. There are 2 types of the virus HIV-1 and HIV-2 and the vast majority of AIDS cases in the U.S and Europe are caused by infection with the retrovirus HIV-1 (retrovirus is an RNA virus that has reverse transcriptase).

HIV structure:
The mature virus consists of an electron dense core containing the viral genome consisting of the 2 short strands of RNA (so they can't replicate outside the living host because there is no DNA). In addition the enzymes reverse transcriptase, protease, ribonuclease, and integrase are present. All are encased by an outer lipid envelope.

1. **Syphilis was a major epidemic before the HIV. This disease has three stages: primary, secondary and tertiary. In the primary we see ulcer in the genitalia. If neglected, it will develop into secondary syphilis that manifest as skin rash and mucosal lesions especially in palms and soles of feet. Syphilis can also affect thoracic aorta causing aneurysm**
2. . **Mechanisms of HIV infection**

The HIV virion expresses a cell surface protein/antigen, gp120, with binding sites for the CD4 molecule on the surface of CD4+T cells. The interaction of viral gp120 with cellular CD4 explains the affinity of HIV for CD4+T cells. In addition, two recognition sites on gp120 for the coreceptors CCR5 (chemokine receptor type 5) and CXCR4 are involved in the entry of HIV into the cell .. In other words, it affects immunity by affecting CD4 and it is important to know the receptors expressed by the virus.

Other CD4+cell types that are targets for HIV infection include monocytes (found in blood and bone marrow), macrophages, dendritic cells, Langerhans cells (Antigen presenting cells found in skin and mucosa) , and microglial cells of the central nervous system (CNS).

i. **Monocytes and macrophages may function as reservoirs for HIV and possibly as vehicles for viral entry into the CNS.**
ii. **HIV may infect neural cells directly by way of CD4 receptors or may compete (through the gp120 protein) for neural receptor sites for neuroleukin, a neural tissue growth factor.**

After cellular binding of gp120 to CD4 and internalization of HIV into the cell, proviral DNA is synthesized by reverse transcription from genomic viral RNA.

In other words:

- **HIV gp120 binds to the CD4 receptor -> viral DNA synthesis happens with the help of reverse transcriptase of the HIV RNA -> a provirus is formed by the host's affected DNA -> the virus is assembled and released with an envelope made by the host's cell membrane.**
- **HIV resembles the HCV in that antibodies are not protective (not a sign of immunity).**
- **ELISA and PCR are used for detection, ELISA detects the antibodies and PCR detect the antigens.**
- **There is a period from time of infection till the time the antibodies appear, so we won't be able to detect antibodies using ELISA.**

NOTE: The probability of infection depends on both the number of infective HIV virions in the body fluid which contacts the host as well as the number of cells with CD4 receptors available at the site of contact.

The enzyme, **reverse transcriptase** which is bound to the HIV RNA helps in the reverse transcription (i.e. conversion) of **RNA to proviral DNA.** It is this HIV proviral DNA which is then inserted into host cell genomic DNA by the **integrase** enzyme.

3. **Establishment of HIV:**
   - Macrophages and Langerhans cells are important both as reservoirs and vectors for the spread of HIV in the body including the CNS. Both macrophages and Langerhans cells can be HIV-infected but are not destroyed themselves. HIV can then be carried elsewhere in the body.
   - Once the infection extends to the lymph nodes, the HIV virions are trapped in the processes of follicular dendritic cells (FDC's), where they provide a reservoir and infect CD4+ T lymphocytes that are passing through the lymph node. The FDC's themselves become infected, but are not destroyed.
   - NOTE: HIV may infect neural cells directly by way of CD4 receptors or may compete (through the gl120 protein) for neural receptor sites for neuroleukin, a neural tissue growth factor.
   - In addition HIV has the ability to **mutate easily**. This high mutation rate leads to the emergence of HIV variants within the infected person's cells that are more toxic and can resist drug therapy. Over time, different tissues of the body may harbor differing HIV variants.

The HIV virus is found in blood, semen, vaginal secretions, breast mild, and saliva. Saliva, urine, tears, & sweat have low count so they rarely cause transmission.

4. **High-risk populations: AIDS**

   a. **Homosexual or bisexual men (75% of cases)**
      i. **The risk is apparently greater with anal receptive intercourse.**
      ii. **In Central Africa, the incidence in both sexes is about equal and is no higher in homosexual or bisexual men than in the general population.**
      iii. **Transmission of HIV can occur from male to male, male to female, and female to male. Female to female transmission remains extremely rare.**

   b. **Intravenous drug abusers (15% of cases). The virus is spread by sharing needles used by infected drug users. Also other instruments like tattoo needles, blood transfusions, and needle puncture of infected blood (in health care workers)**

c. **Heterosexual partners of persons in high-risk groups (4% of cases). Sexual transmission from intravenous drug abusers is the major mode of entry of HIV into the heterosexual population.**

d. **Patients receiving multiple blood transfusions (2% of cases). Risk has been greatly diminished by screening donor blood for anti-HIV antibodies, HIV p24 antigen and HIV-1 RNA.**

e. **Hemophiliacs (1% of cases). Most likely, the entire cohort of hemophiliac who received factor VIII concentrates between 1981 and 1985 became infected with HIV. Since 1985, HIV screening and heat inactivation of HIV in factor VIII concentrates have become universal.**

f. **Infants of high-risk parents. Infection can be transplacental or can occur at the time of delivery.**

Note: HIV infection is not spread by casual contact in public places, households, or in the workplace. HIV is not spread by insect vectors. There is **no vaccine** to prevent HIV infection.

5. Diagnosis of HIV
   - **Diagnosis by the ELISA test is presumptive; follow-up tests include molecular techniques like: Western blot and direct assessment of viral RNA.**
   - **NOTE: The average HIV-infected person may take up to several weeks to become seropositive, and then may live up to 8 or 10 years, on average, before development of the clinical signs and symptoms of AIDS.**

   - Start with Elisa which is a screening test
   - Then, with Western blot which is a confirmatory test. (It looks for viral RNA) or immunofluorescence assay (IFA)
   - For Follow up: We count CD4 / CD48 ratio normally range from 1 to 4 if less than 1 so abnormal and we try to restore it by HIV treatment

6. Stages of HIV Infection

HIV disease may be asymptomatic for many years. Before fully developed AIDS occurs, there is a primary infection which may go unnoticed or can cause acute illness resembling infectious mononucleosis (flu infection)(diminish over 1 to 2 months); a long latent phase(2-20 years) followed by generalized lymphadenopathy; and a stage marked by chronic fever, weight loss, and diarrhea. (Appears first like a transient flu like illness)

a. **HIV seropositivity begins soon after initial HIV infection. Antibodies to the proteins coded by the genes of retroviral *gag, env,* and *pol* regions can be demonstrated, especially antibodies to the gp120 and p24 proteins. HIV**

infection can also be demonstrated by amplification of viral genetic sequences by polymerase chain reaction or by viral culture.

b. **The last stage, defined as AIDS, is marked by HIV infection complicated by specified secondary opportunistic infection or malignant neoplasms**.

- **The primary target of HIV is the immune system, which is gradually destroyed.**
- **Clinically, HIV infection may appear "latent" for years. During this period there is ongoing immune system destruction but still enough of the immune system remains intact to provide immunity and prevent most infections.**
- **Eventually, when a significant number of CD4+ T lymphocytes have been destroyed and when production of new CD4 cells cannot match destruction, then failure of the immune system leads to the appearance of clinical AIDS**
- **The CD4+T cells to CD8+T cells ratio is also greatly reduced, often to less than 1.0.**

7. Pathogenesis of AIDS

- **Progression to clinical AIDS is also marked by the appearance of syncytia-forming (SI) variants of HIV in about half of HIV infected patients. These SI viral variants have greater attraction to CD4 cells and are associated with more rapid CD4+ cell decline.**

- **Infection with HIV results in the depletion of CD4+ T cells. The number of circulating lymphocytes is greatly decreased and this decrease is accounted for by a loss of CD4+ T cells. (fall in CD4 count to <200 cells/mm3. Depletion of CD4 is the key feature of AIDS).**
- **The CD4+:CD8+ ratio is also greatly reduced, often to less than 1.0.**
- **The stage of clinical AIDS is reached years after initial infection and is marked by the development of one or more of the typical opportunistic infections or neoplasms common to AIDS.**

Following are some of the more common complications seen with AIDS:

a. ***Pneumocystis carinii* pneumonia** is the most common **opportunistic infection in patients with (AIDS);** it also occurs in other forms of immunodeficiency.it commonly produces a **pulmonary infection.**

i. It is caused by *P. carinii* (recently renamed *Pneumocystis jiroveci),* which is now classified as a fungus. **Comma shaped organism**

ii. Diagnosis is by morphologic demonstration of the organism in biopsy of lung (transbronchial biobsy) or bronchial washing (bronchoalveolar lavage) specimens. **(The exudates is soap-bubble like)**

b. **Mycobacterial** infections are frequently seen with AIDS.
Mycobacterium tuberculosis, Mycobacterium avium complex (MAC) infection.Definitive diagnosis of mycobacterial disease is made by culture and PCR.

c. **Cytomegalovirus** (CMV) infection is seen with AIDS. It causes pneumonia and it can also cause serious disease in the brain and gastrointestinal tract. It is also a common cause for retinitis and blindness in persons with AIDS.

d. **Fungal infections**
   - Candidiasis of the esophagus, trachea, bronchi, or lungs.
   - Cryptococcus neoformans (produces pneumonia and meningitis), Histoplasma capsulatum, and Coccidioides immitis.

Others:

Herpes Simplex encephalitis or dermatitis,**Toxoplasmosis** caused by *Toxoplasma gondii* is a protozoan parasite that most often leads to infection of the brain with AIDS**, Herpes simplex** infection in the mucosa**, Aspergillosis** especially in the lung, **Cryptosporidium and Microsporidium** produce voluminous watery diarrhea in patients with AIDS. **Viral** HIV encephalitis**, Syphilis** (primary, secondary and tertiary)

e. Increased incidence of malignancy, particularly multifocal **Kaposi sarcoma,** an otherwise rare lesion that in AIDS is almost entirely confined to the homosexual male population. KS. Produces reddish purple patches or nodules over the skin and can be diagnosed with skin biopsy. Visceral organ can also be involved with KS.It is a sarcoma of the blood vessels. **Kaposi sarcoma is a tumor of the endothelial cells, most of the time it is caused by Human Herpes Virus Type 8.**

f. Malignant lymphomas like B-cell **non-Hodgkin lymphoma.** They are typically of a high grade and often in the brain. They are very aggressive and respond poorly to therapy. an increased incidence of Hodgkin disease and hepatocellular carcinoma also occurs.

g. **Lymphoid interstitial pneumonitis** (LIP) is a condition involving the lung that can be seen in AIDS in children.

h. **Central and peripheral nervous system manifestations** occur due to

Before AIDS was found in 1981: most important STDs were Syphilis and gonorrheal infection.

Syphilis is divided into :

Primary: characterized by presence of ulcer on the external genitalia. Ulcer can heal spontaneously.

Secondary: This appears after many years if the treatment was insufficient. It is characterized by skin rash affecting also the palm and sole of foot. (under the microscope there are plasma cells around blood vessels in the dermis)

Summary!

AIDS is the end stage of a disease caused by human immuno-deficiency virus (HIV) infection There are 2 types of the virus HIV-1 and HIV-2 and the vast majority of AIDS cases are caused by infection with the retrovirus HIV-1.

Mechanisms of HIV infection: the HIV virion expresses a cell surface protein, gp120 with binding sites for the CD4 +T cells. After cellular binding of gp120 to CD4 and internalization of HIV into the cell, proviral DNA is synthesized by reverse transcription from genomic viral RNA.

High-risk populations: AIDS

1. Homosexual or bisexual men (75% of cases)

2. Intravenous drug abusers (15% of cases).

3. Heterosexual partners of persons in high-risk groups (4% of cases).

4. Patients receiving multiple blood transfusion (2% of cases).

5. Hemophiliacs (1% of cases).

6. Infants of high-risk patients.

Pathogenesis of AIDS: infection with HIV results in the depletion of CD4+ T cells.

Clinical features: opportunistic infections, neoplasms, CNS manifestation.

Opportunistic infections: *Pneumocystis carinii* pneumonia (recently renamed *Pneumocystis jiroveci*) is the most common opportunistic infection in patients with acquired immunodeficiency syndrome.

Neoplasms: particularly multifocal hemorrhagic Kaposi sarcoma, caused by Human Herpes Virus 8. Markers: HHV8 and CD34 (related to endothelial proliferation) are positive. Histologically: it has spindle cells with RBCs in between. , and malignant B-cell non-Hodgkin lymphoma.

Stages of HIV infection: HIV disease may be asymptomatic for many years. Before fully developed AIDS occurs, there is acute illness resembling infectious mononucleosis (flu infection); a long latent phase (2-20 years) asymptomatic followed by generalized lymphadenopathy; and a stage marked by chronic fever, weight loss and diarrhea.

Questions

1- Which one of these populations are at highest risk of developing AIDS?

A-IV drug abusers
B-Patients receiving multiple blood transfusions
C-Homosexual/bisexual men

2-what is the most common opportunistic infection in patients with acquired immunodeficiency syndrome?

A-syphilis
B- Pneumocystis jiroveci
C-gonorrhea