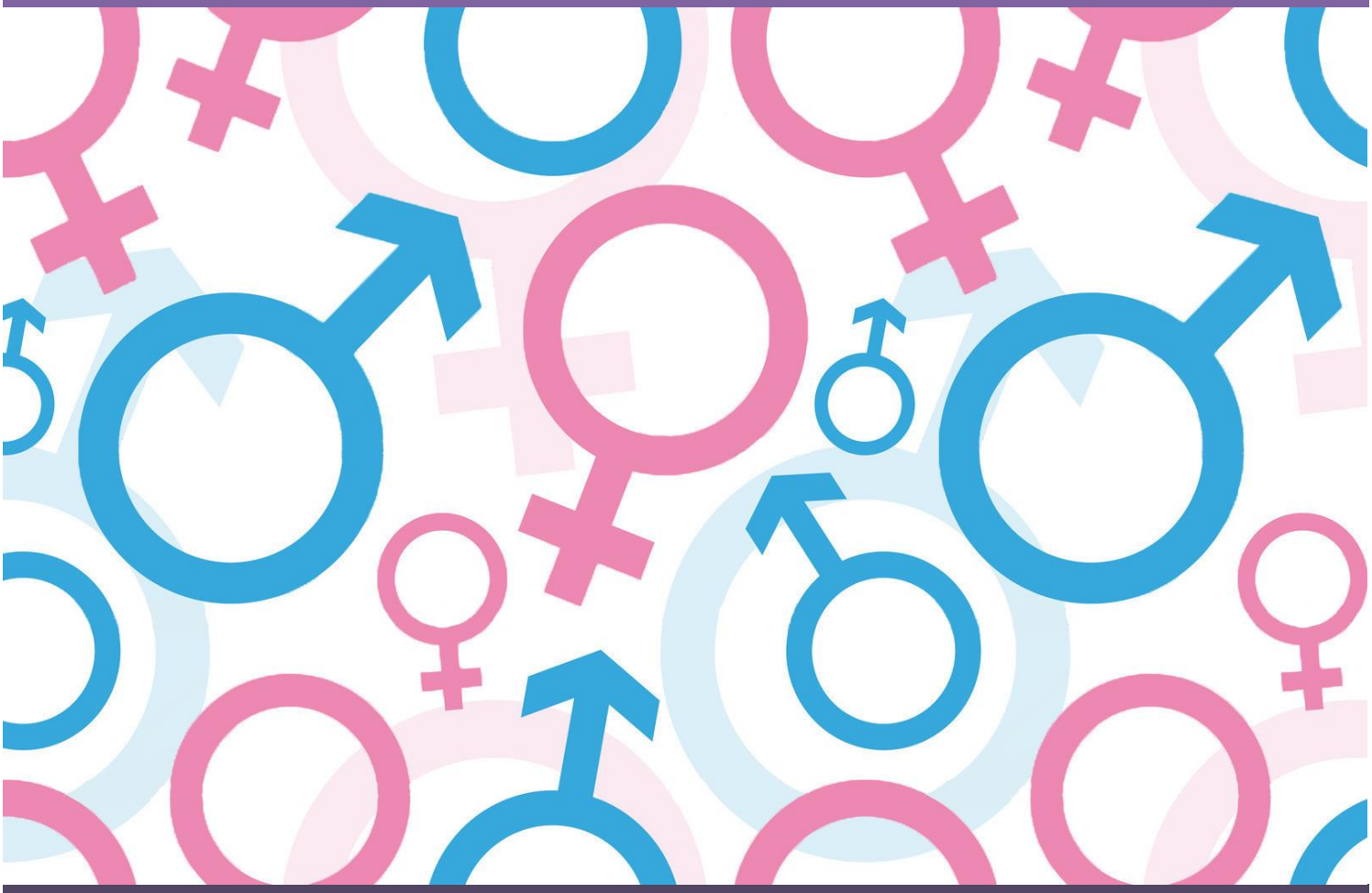


Lecture 10

Systemic Manifestations of AIDS

*432 **Pathology** Team*

***Done By: Abdulhameed** Al-Saawy*

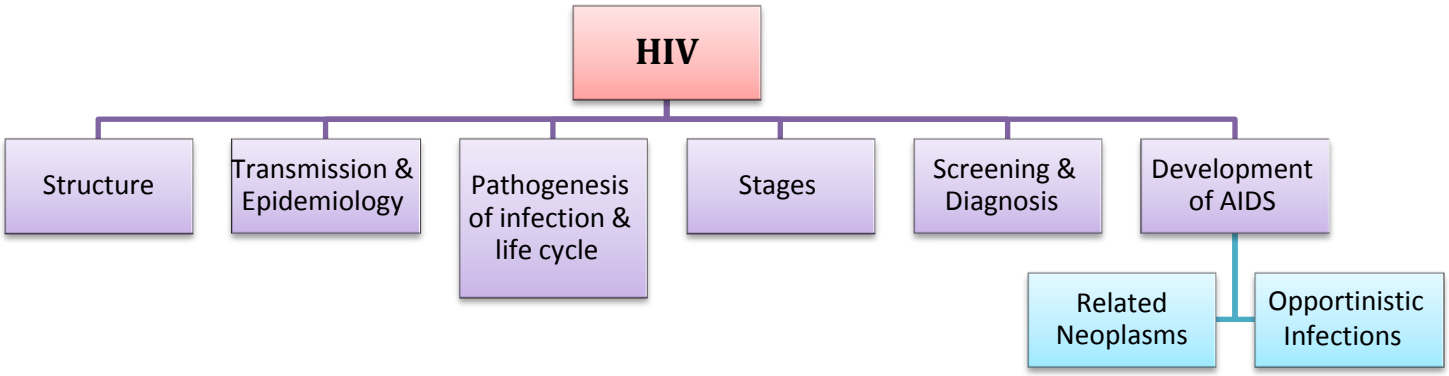
***Reviewed By: Rawan** AL-Taleb*

Reproductive Block

Color Index: Female notes are in Green. Male notes are in Blue. Red is important. Orange is explanation.

HIV

Mind Map:



NOTE: **Dr. Ammar spent the first 20 minutes of his lecture on STDs in general especially Hepatitis B, HPV, HSV, Chlamydia and Gonorrhea.**

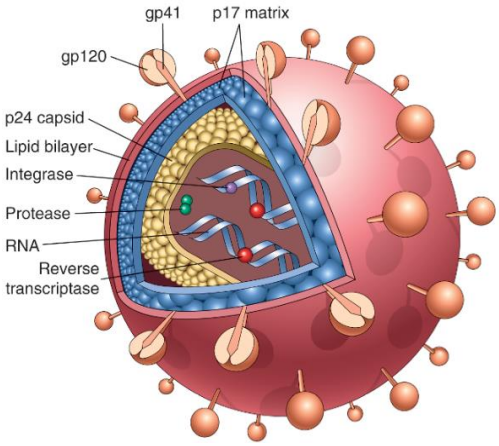
We advise you to at least go through them, but we are sure that the pathology questions of this lecture in the exam will not be concerning them.

Introduction:

- Human immunodeficiency virus (HIV) is the causative agent for AIDS.
- HIV is caused by a retrovirus **(contains the enzyme reverse transcriptase)** of the lentivirus family that contains only RNA.
- It was unknown until the early 1980's, but since then has been spread around the world to infect millions of persons.
- The most common type of HIV infections is known as HIV-1 and is the type that has led to the worldwide AIDS epidemic.
- There is also an HIV-2 that is much less common. **(principally in west Africa)**
- The result of HIV infection is the destruction of the immune system.
- All HIV infected persons are at risk for illness and death from development of opportunistic infections and tumors and the inevitable manifestations of AIDS.

HIV Structure:

- The mature virus consists of an electron dense core containing the viral genome consisting of the 2 short strands of RNA (ribonucleic acid). In addition the enzymes reverse transcriptase, protease, ribonuclease, and integrase are present. All are encased by an outer lipid envelope.
- The virus core also contains (1) major capsid protein p24 (antibodies to p24 are important. For screening and diagnosis), (2) nucleocapsid protein p7/p9. The viral core is surrounded by a matrix protein called p17, lying beneath the virion envelope. The viral envelope itself is studded with two viral glycoproteins (gp120 and gp41), critical for HIV infection of cells.



Epidemiology and transmission:

- The virus is found in blood, semen, vaginal secretions, breast milk and Saliva.
- Transmission of HIV occurs under conditions that facilitate the exchange of blood or body fluids that contain the virus or virus-infected cells.
- Thus, the major routes of HIV infection are sexual contact (75%), parenteral inoculation, and passage of the virus from infected mothers to their newborns.
- HIV infection is not spread by casual contact in public. HIV is not spread by insect vectors. There is no vaccine to prevent HIV infection **(due to its high mutation rate)**

NOTE: saliva, urine, tears, and sweat is of no major clinical importance, as transmission of HIV through these fluids does not routinely occur because of the low concentration of HIV in these fluids.

Sexual Transmission:

- Sexual transmission is by far the major mode of infection worldwide, accounting for more than 75% of all cases of HIV transmission.
- Transmission of HIV can occur from male to male, male to female, and female to male. Female to female transmission remains extremely rare.
- The virus is present in semen, both extracellularly and within mononuclear inflammatory cells, and it enters the recipient's body through lacerations or abrasions in mucosa.
- Clearly, all forms of sexual transmission are aided and abetted by the concomitant presence of other sexually transmitted diseases that cause genital ulcerations.
- STDs are also cofactors for HIV transmission, primarily by increasing the seminal fluid content of inflammatory cells (presumably carrying HIV).

Parenteral Transmission:

- Parenteral transmission of HIV is well documented in three different groups: intravenous drug abusers (the largest group), hemophiliacs receiving factor VIII or IX concentrates, and random recipients of blood transfusion.

Mother-to-Infant Transmission:

- Mother-to-infant vertical transmission is the major cause of pediatric AIDS.
- Three routes are involved: in utero, by transplacental spread; intrapartum, during delivery; and by ingestion of HIV-contaminated breast milk.

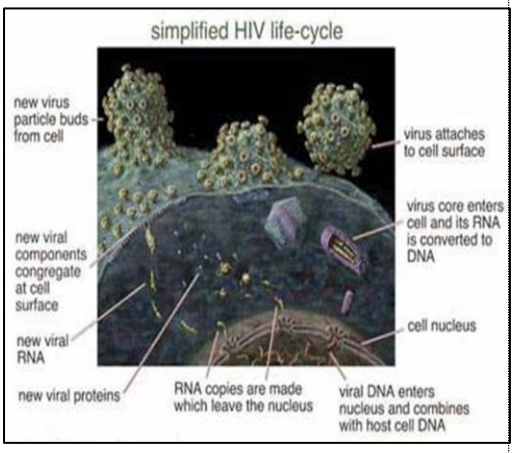
High-risk populations:

- Homosexual or bisexual men (75% of cases in the US)
  - The risk is apparently greater with anal receptive intercourse.
  - 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.
- Intravenous drug abusers (15% of cases).
  - The virus is spread by sharing needles used by infected drug users.
- 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.
- 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.
- 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 diminishing its spread.
- Infants of high-risk parents.

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.

Pathogenesis of infection & life cycle of the virus:

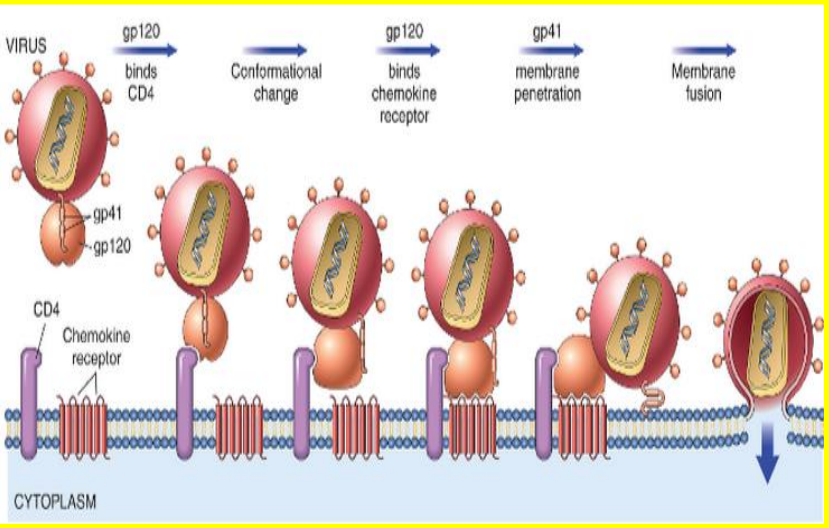
- The glycoprotein gp120 has binding sites for the CD4 molecule on the surface of CD4+ve cells.
- The interaction of viral gp120 with cellular CD4 explains the affinity of HIV for CD4+ve cells.
- The probability of infection depends on both the number of infective HIV virions in the body fluid which contacts the host as well as the number of cells with CD4 receptors available at the site of contact.
- It also has recognition sites for the co-receptors **(may also be called chemokine receptors)** CCR5 and CXCR4 (only on T which are involved in the entry of HIV into the Cell.
- Other CD4+cell types that are targets for HIV infection include monocytes, macrophages, 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.
- Monocytes, macrophages and Langerhans may function as reservoirs for HIV and possibly as vehicles for viral entry into 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.
- HIV may infect neural cells directly by way of CD4 receptors or may compete (through the gpl20 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 **(function of reverse transcriptase)** from viral RNA.
- This HIV proviral DNA is then inserted into host cell genomic DNA by the **integrase** enzyme.
- Once the HIV proviral DNA is within the infected cell's genome the HIV provirus is replicated by the host cell to produce additional HIV virions which are released by surface budding or after cell lysis.

Summary for the infection from Robbins:

•HIV envelope gp120 binds initially to CD4 molecules. This binding leads to a conformational change that exposes a new recognition site on gp120 for the coreceptorsCXCR4 (mostly on T cells) or CCR5 (mostly on macrophages). The gp41 then undergoes a conformational change that allows it to insert into the target membrane, and this process facilitates fusion of the virus with the cell. After fusion, the virus core containing the HIV genome enters the cytoplasm of the cell. FIGURE



Stages of HIV Infections:

- Primary HIV infection may go unnoticed in at least half of cases or produce a mild disease which quickly subsides,or produces acute HIV infection, followed by a long clinical "latent" period lasting years.
- Primary acute HIV infections may include fever, generalized lymphadenopathy, pharyngitis, rash, arthralgia and diarrhea. These symptoms diminish over 1 to 2 months.
- The average HIV-infected person may take up to several weeks to become seropositive (3-7 weeks), and then may live up to 8 or 10 years, on average, before development of the clinical signs and symptoms of AIDS.
- HIV seropositivity: 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.

Diagnosis of HIV

- Test for HIV antibodies is done with a rapid test using an enzyme-linked immunosorbent assay (ELISA) technique.
- If positive, then the next step is to:
  - Confirm infection with Western blot or immunofluorescence assay IFA.
- HIV infection can also be demonstrated by amplification of viral genetic sequences by PCR or by viral culture.
- 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.

AIDS

Pathogenesis of AIDS:

- Infection with HIV results in the depletion of CD4+ cells.
- The number of circulating lymphocytes is greatly decreased, and this decrease is accounted for by a loss of CD4+T cells.
- The CD4+:CD8 ratio (Normally 2:1) is greatly reduced, often to less than 1.
- When the number of T-cells decreases to lower than 200/microliter the patient develops full blown AIDS. This is the point at which the characteristic opportunistic infections and neoplasms of AIDS appear.
- 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 development of chronic infections (e,g. herpes) leads to rapid progression into AIDS. **(activation of the immune system leads to increased rate of replication of viral genome in activated T-cells causing more cell death)**
- Reactivation of dormant latent TB is very common.
- The 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 are associated with more rapid CD4+ cell decline. **(Formation of syncytia (giant cells): In tissue culture, the gp120 expressed on productively infected cells binds to CD4 molecules on uninfected T cells, followed by cell fusion, ballooning, and death within a few hours).**
- The development of signs and symptoms of AIDS typically parallels laboratory testing for CD4 lymphocytes. **(inversely related)**

Clinical AIDS:

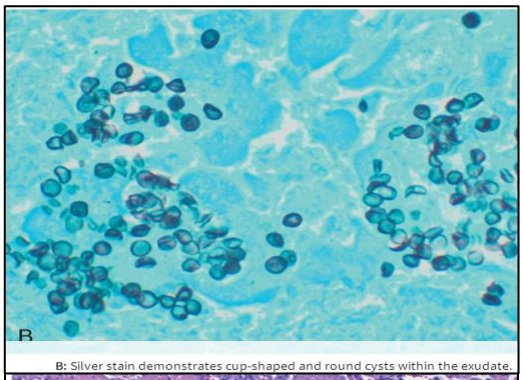
- Characterized by the development of opportunistic infections, secondary neoplasms and CNS involvement.
- Miscellaneous: e.g. lymphoid interstitial pneumonitis is a condition involving the lung that can be seen in AIDS in children.

1- Opportunistic infections:

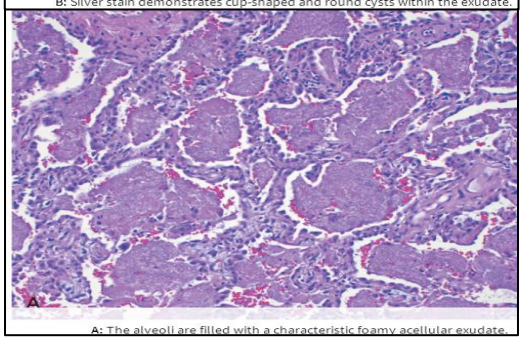
Pneumocystis jiroveci

- Pneumocystis jiroveci (formerly carinii) is the most frequent opportunistic infection seen with AIDS. It commonly produces a pulmonary infection.

- Diagnosis is made histologically by finding the organisms in cytologic (bronchoalveolarlavage) or biopsy (transbronchial or open lung biopsy) material from lung.(shows soap bubble pattern"cotton candy exudate", and silver staining shows the organism which is comma shaped)



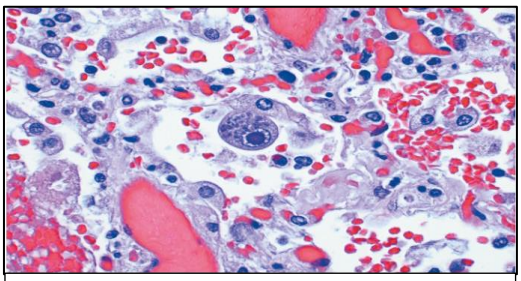
B: Silver stain demonstrates cup-shaped and round cysts within the exudate.



A: The alveoli are filled with a characteristic foamy acellular exudate.

Cytomegalovirus

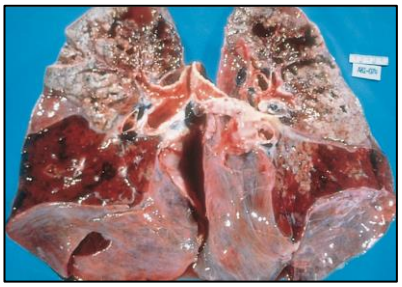
- Cytomegalovirus (CMV) infection is seen with AIDS. It causes pneumonia and it can also cause serious disease in the brain and gastrointestinal tract. It is also a common cause for retinitis and blindness in persons with AIDS. (it causes diarrhea and delirium)



Affected cells are strikingly enlarged, often to a diameter of 40µm, and exhibit cellular and nuclear polymorphism.

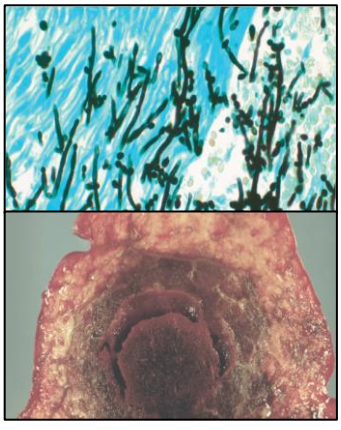
Mycobacterial infections

- In AIDS patients it's mostly caused by atypical mycobacteria. (MAC, M.Leprae …etc)
- It starts in the apical lobe.
- Mycobacterium avium complex (MAC)(also called mycobacterium avium-intracellulare) infection.
- Definitive diagnosis of mycobacterial disease is made by culture and PCR.



Fungal Infections

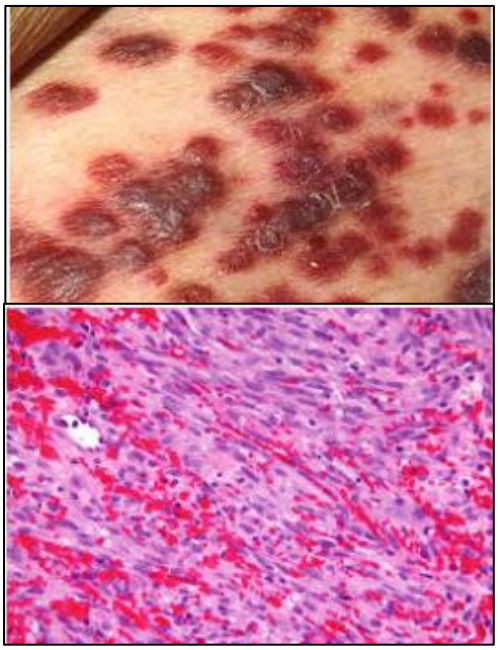
- Candidiasis of the esophagus, trachea, bronchi, or lungs.
- Fig. pseudohyphae and budding yeast on silver stain (candida)
- Aspergillosis especially in the lung
- Cryptococcusneoformans (produces pneumonia and meningitis), Histoplasmacapsulatum, and Coccidioidesimmitis.



Other infections

- 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.
- Cryptosporidium and Microsporidium produce voluminous watery diarrhea in patients with AIDS.
- Viral encephalitis.
- Syphilis (primary, secondary and tertiary).

2- Malignant Neoplasms



Kaposi's sarcoma (KS)

- It is a sarcoma of the blood vessels.
- Kaposi sarcoma is caused by a herpesvirus called Kaposi sarcoma herpesvirus (KSHV), or human herpesvirus-8 (HHV-8).
- Produces reddish purple patches or nodules over the skin and sometimes the gums and can be diagnosed with skin biopsy.
- On histological examination it shows hyperplasia of pleomorphic spindle cells and areas of hemorrhage.
- Visceral organ can also be involved with KS.

Malignant lymphomas

- Commonly it **is B-cell Non Hodgkins Lymphoma.**
- They are typically of a high grade, very aggressive and respond poorly to therapy.
- The brain is the most common extranodal site in late-stage HIV infection, and hence primary lymphoma of the brain is considered an AIDS-defining condition.
- Close to 100% of these brain lymphomas are EBV-related.

CNS involvement

- Involvement of the CNS is a common and important manifestation of AIDS.(may be the first presentation for the patient)
- Most commonly a progressive encephalopathy clinically designated the AIDS dementia complex

Miscellaneous e.g. lymphoid interstitial pneumonitis is a condition involving the lung that can be seen in AIDS in children.

Summary from Robbins:

Human Immunodeficiency Virus Life Cycle and the Pathogenesis of AIDS

- **Virus entry into cells: requires CD4 and co-receptors, which are receptors for chemokines; involves binding of viral gp120 and fusion with the cell mediated by viral gp41 protein; main cellular targets: CD4+ helper T cells, macrophages, DCs**
- **Viral replication: integration of provirus genome into host cell DNA; triggering of viral gene expression by stimuli that activate infected cells (e.g., infectious microbes, cytokines produced during normal immune responses)**
- **Progression of infection: acute infection of mucosal T cells and DCs; viremia with dissemination of virus; latent infection of cells in lymphoid tissue; continuing viral replication and progressive loss of CD4+ T cells**
- **Mechanisms of immune deficiency:**
- **Loss of CD4+ T cells: T cell death during viral replication and budding (similar to other cytopathic infections); apoptosis occurring as a result of chronic stimulation; decreased thymic output; functional defects**
- **Defective macrophage and DC functions**
- **Destruction of architecture of lymphoid tissues (late)**

Summary

Mode of transmission	Sexual transmission	Parenteral transmission	Mother-to-Infant Transmission
Notes	The virus is present in semen, both extracellularly and within mononuclear inflammatory cells STDs are also cofactors for HIV transmission	-Intravenous drug abusers -Hemophiliacs receiving factor VIII or IX concentrates -Blood transfusion	Is the major cause of pediatric AIDS. Three routes are involved: in utero, intrapartum and breast feeding
Pathogenesis of HIV	HIV envelope gp120 binds initially to CD4 molecules. This binding leads to a conformational change that exposes a new recognition site on gp120 for the coreceptorsCXCR4 (mostly on T cells) or CCR5. The gp41 then undergoes a conformational change that allows it to insert into the target membrane, and this process facilitates fusion of the virus with the cell. After fusion, the virus core containing the HIV genome enters the cytoplasm of the cell		
Pathogenesis of AIDS	The number of circulating lymphocytes is greatly decreased, and this decrease is accounted for by a loss of CD4+T cells. The CD4+:CD8 ratio (Normally 2:1) is greatly reduced, often to less than 1. When the number of T-cells decrease to lower than 200/microliter the patient develops full blown AIDS. This is the point at which the characteristic opportunistic infections and neoplasms of AIDS appear. 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.		
Opportunistic infections	**Pneumocystis jiroveci** is the most frequent opportunistic infection seen with AIDS. It commonly produces a pulmonary infection. histological finding (shows soap bubble pattern, and silver staining shows the organism which is comma shaped)	**Cytomegalovirus** 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	**Mycobacterial infections** In AIDS patients it's mostly caused by atypical mycobacteria. (MAC, M.Leprae …etc) It starts In the apical lobe.
Malignant Neoplasm	**Kaposi's sarcoma (KS)** It is a sarcoma of the blood vessels. Kaposi sarcoma is caused by a human herpesvirus-8 (HHV-8). Produces reddish purple patches or nodules over the skin. Can be diagnosed with skin biopsy. On histological examination it shows hyperplasia of pleomorphic spindle cells and areas of hemorrhage.	**Malignant lymphomas** Commonly it is B-cell Non Hodgkins Lymphoma. They are typically of a high grade, very aggressive and respond poorly to therapy. The brain is the most common extranodal site in late-stage HIV infection	**CNS involvement** Most commonly a progressive encephalopathy clinically designated the AIDS dementia complex

Questions

1/ A 45-year-old man presents with painful, purple nodules on the dorsal surface of his left hand that he first noticed 9 months ago. A biopsy discloses a poorly demarcated lesion composed of atypical spindle-shaped neoplastic cells and extravasated red cells. Similar lesions are found in the lymph nodes and liver. Which of the following viruses is associated with the pathogenesis of these skin lesions?

(A) Cytomegalovirus
(B) Epstein-Barr virus
(C) Herpes simplex virus type 2
(D) Human herpesvirus type 8

2/ A 31-year-old man with AIDS Presents with fever, dry cough and shortness of breath. Transbronchial biopsy is done and shows soap bubble pattern. What is the most likely diagnosis?

(A) Pneumocystis jiroveci
(B) Kaposi's sarcoma
(C) Mycobacterial infection
(D) Lymphoid interstitial pneumonitis

3/ Which of the following enzymes converts the HIV genome into double-stranded DNA in host cells in the patient described in Question 2?

(A) DNA polymerase (Pol-1)
(B) DNA polymerase (Pol-2)
(C) Integrase
(D) Reverse transcriptase

Answers:

- 1- D
- 2- A
- 3- D

اللهم إني استودعك ما قرأت و ما حفظت و ما تعلمت فرده عليَ عند حاجتي إليه انك على كل شيء قدير

If there is any mistake or feedback please contact us on: 432PathologyTeam@gmail.com

"إن أصبنا فمن الله، وإن أخطأنا فمن أنفسنا والشيطان"

بهذا العمل نختتم أعمالنا النظرية بحمد الله وتوفيقه، وكل الشكر لكم على ماقدمتموه لنا من ثقة ووقت وجهد. نسأل الله أن يجعله في موازين حسناتكم

شكرا لكم!

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