



Systemic Manifestations of AIDS

Lecture 10

430 Pathology Team

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Red: Doctors' and important notes.
Green: Team notes.

Acquired Immunodeficiency Syndrome (AIDS):

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)**.

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.

Mechanisms of HIV infection:

- A. The HIV virion expresses a cell surface protein, **gp120 with binding sites for the 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 co-receptors CCR5 (**chemokine receptor type 5**) and CD4R4 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.**
- B. 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 the skin and mucosa**) and **microglial cells of the central nervous system (CNS)**.
 1. Monocytes and macrophages may function as reservoirs for HIV and possibly as vehicles for viral entry into the CNS.
 2. 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.
- C. 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.
- D. The HIV virus is found in blood, semen, vaginal secretions, breast milk and saliva.
 - E. Diagnosis by the ELISA test is presumptive; follow-up tests include molecular techniques like: Western blot and direct assessment of viral RNA.

High-risk populations: AIDS

- A. **Homosexual or bisexual men** (75% of cases)
 - 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.
- B. **Intravenous drug abusers** (15% of cases). The virus is spread by sharing needles used by infected drug users.

- 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 group 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 patients.** Infection can be transplacental or can occur at time of delivery.

Pathogenesis of AIDS:

- A.** 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.

Clinical features:

1. Opportunistic infections:

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

1. It is caused **by *P. carinii* (recently renamed *Pneumocystis jirovecii*)**, which is now classified as a fungus.
2. Diagnosis is by morphologic demonstration of the organism in biopsy (stained by silver stain) or bronchial washing specimens (lavage).

AIDS-Defining Opportunistic Infections

Infections

PROTOZOAL AND HELEMINTHIC INFECTIONS

Cryptosporidiosis or isosporidiosis (enteritis)
Pneumocystosis (pneumonia or disseminated infection)
Toxoplasmosis (pneumonia or CNS infection)

FUNGAL INFECTIONS

Candidiasis (esophageal, tracheal or pulmonary)
Cryptococcosis (CNS infection) (**necrosis and cyst formation**)
Aspergillosis
Coccidioidomycosis (disseminated)
Histoplasmosis (disseminated)

BACTERIAL INFECTIONS

Mycobacteriosis ("atypical" e.g., mycobacterium avium-intracellulare, disseminated or extrapulmonary; M. tuberculosis, pulmonary or extra pulmonary)
Nocardiosis (pneumonia, meningitis, disseminated)

VIRAL INFECTIONS

Cytomegalovirus (pulmonary, intestinal, retinitis, or CNS infections)
Herpes simplex virus (localized or disseminated) (**large nuclei resembling puzzles**)
Syphilis (Primary, secondary and tertiary).
Varicella-zoster virus (localized or disseminated)
Progressive multifocal leukoencephalopathy

2. **Neoplasms:** particularly multifocal hemorrhagic Kaposi **sarcoma**, found on limbs and it is caused by **Human Herpes Virus 8** an otherwise rare lesion that in AIDS is almost entirely confined to the homosexual male population. **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**; an increased incidence of Hodgkin's disease and hepatocellular carcinoma also occurs.

AIDS-Defining Neoplasms

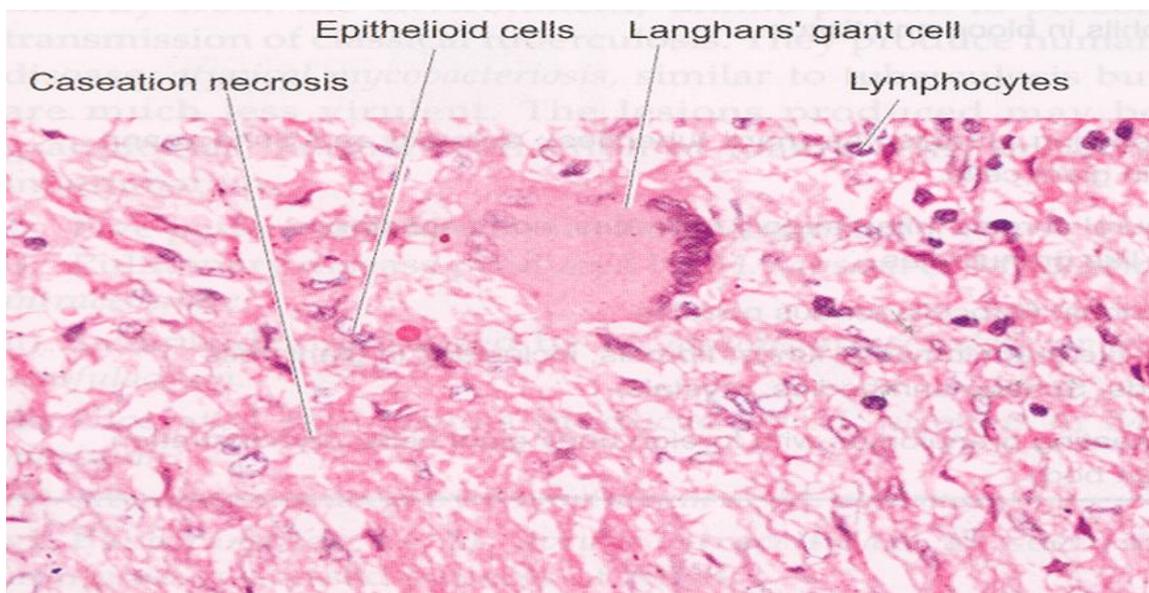
Kaposi sarcoma
Non-Hodgkin lymphoma (Burkitt, immunoblastic)
Primary lymphoma of brain
Invasive cancer of uterine cervix

3. **Central and peripheral nervous system manifestations** occur due to opportunistic infections such as Toxoplasmosis and Cryptococcus, CNS tumors, or direct neural infection with HIV.

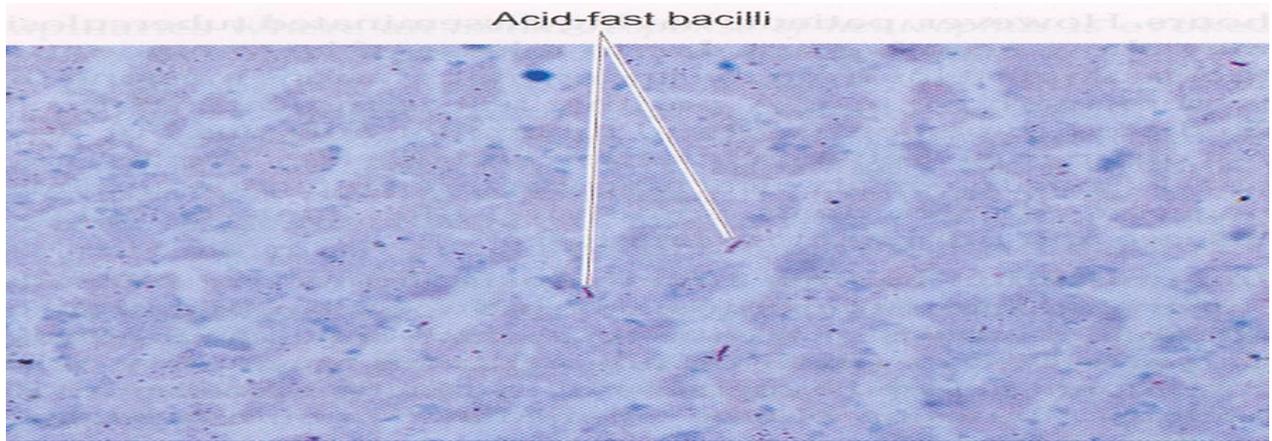
Stages of HIV infection

HIV disease has 4 stages: first 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.

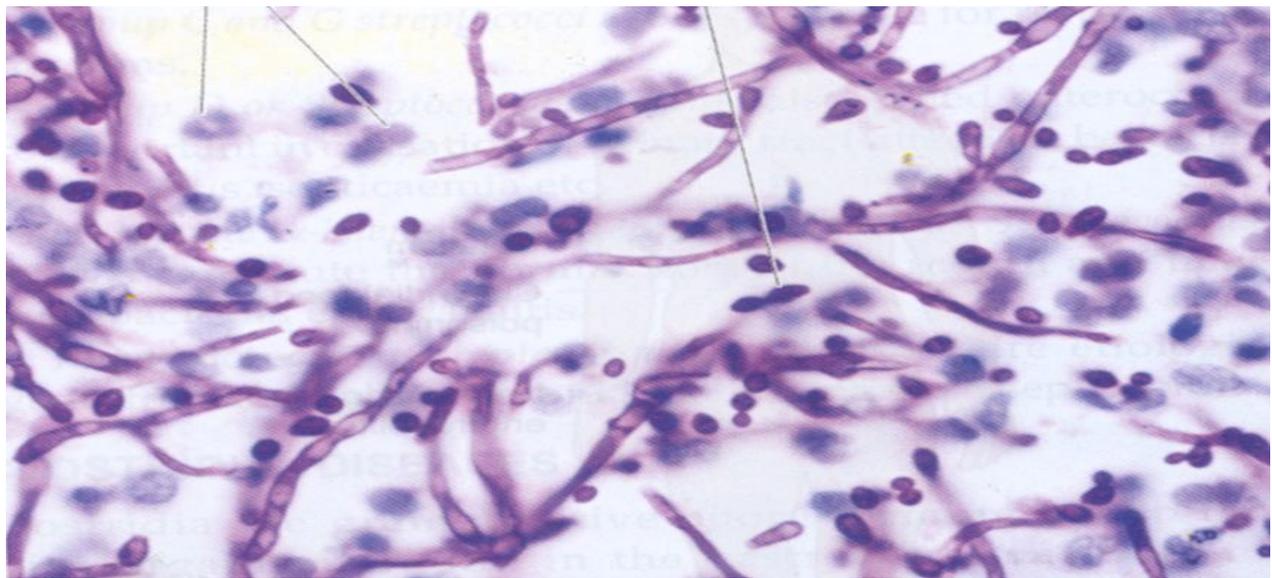
- A. **HIV seropositivity** begins soon after initial HIV infection. Antibodies to the proteins coded by the genes of retroviral gag, env and pol regions can be demonstrated, especially antibodies to the gp120 and p24 proteins. HIV infection can also be demonstrated by amplification of viral genetic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



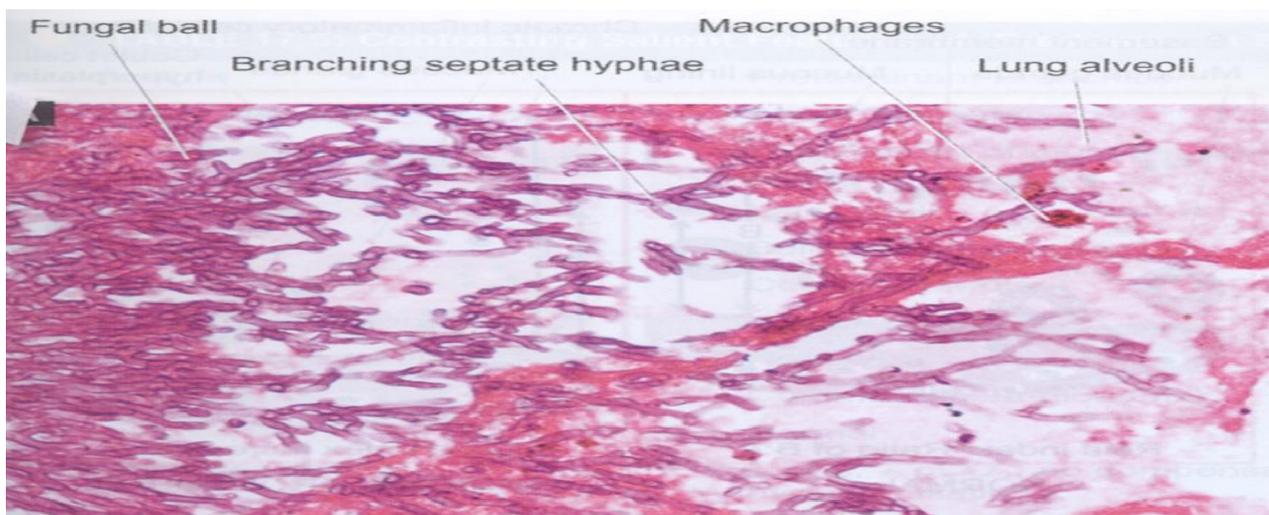
Morphology of a tubercle



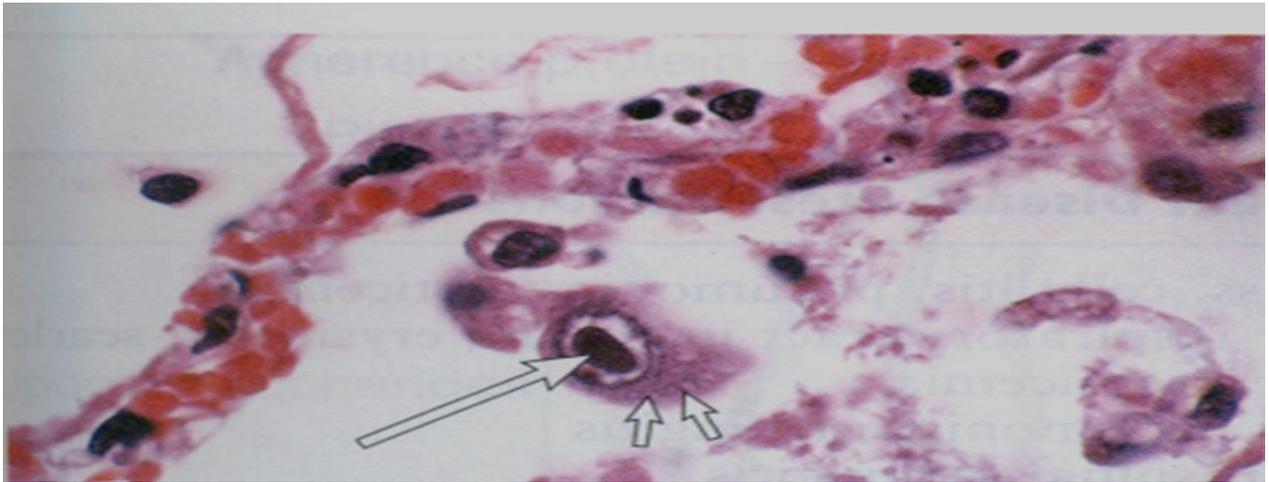
Tuberculosis of the lymph nodes showing presence of acid-fast bacilli in Ziehl-Neelsen staining



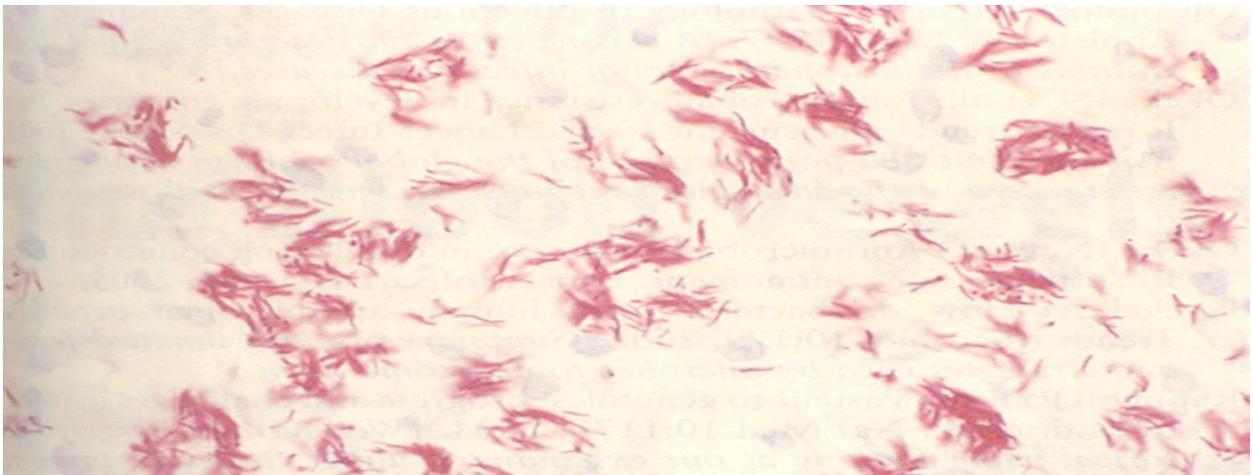
Candidiasis of the ulcer in the skin. The diagnosis is made by observing the characteristics pseudohyphae and blastoconidia (budding yeast).



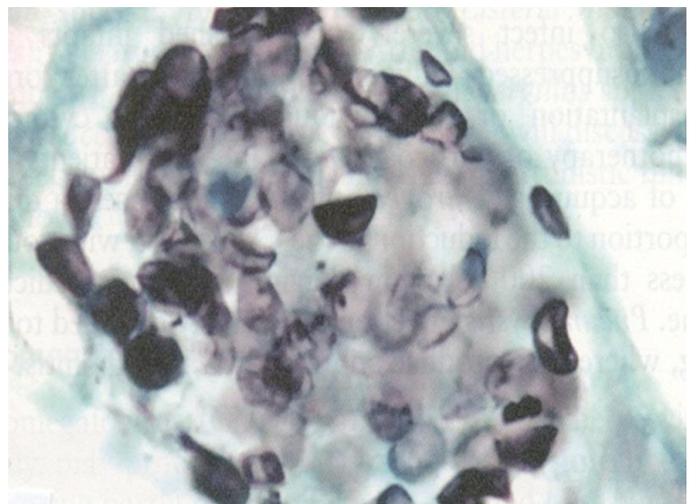
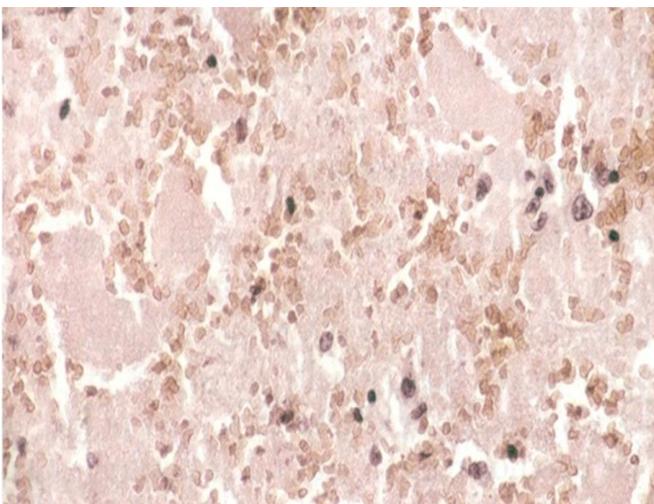
Aspergillosis of the Lung



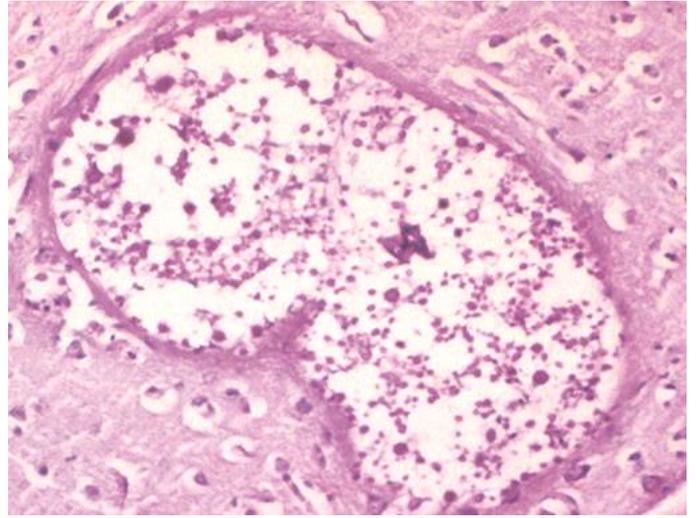
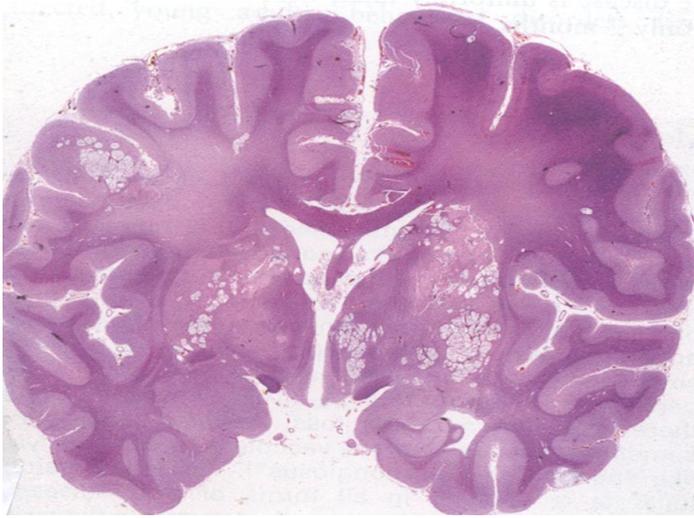
Cytomegalovirus infection of the lung. A typical distinct nuclear and ill-defined cytoplasmic inclusion is seen



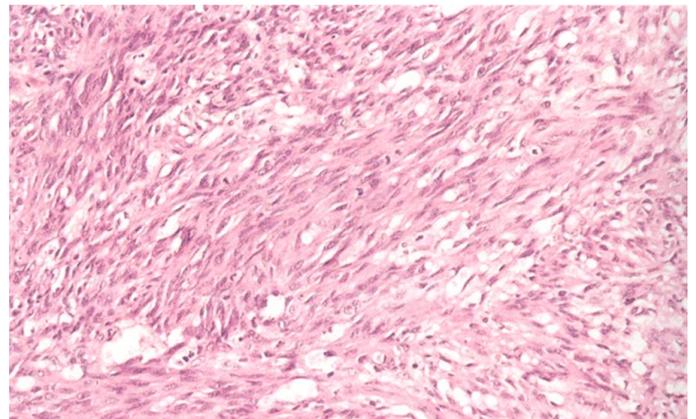
Host responses in the absence of appropriate T cell-mediated immunity. There is no granuloma response; the intracellular bacteria persist and proliferate within the macrophages because of inadequate T cells. Mycobacterium avium infection showing massive intracellular macrophages with acid-fast organisms (filamentous and pink in acid-fast stain)



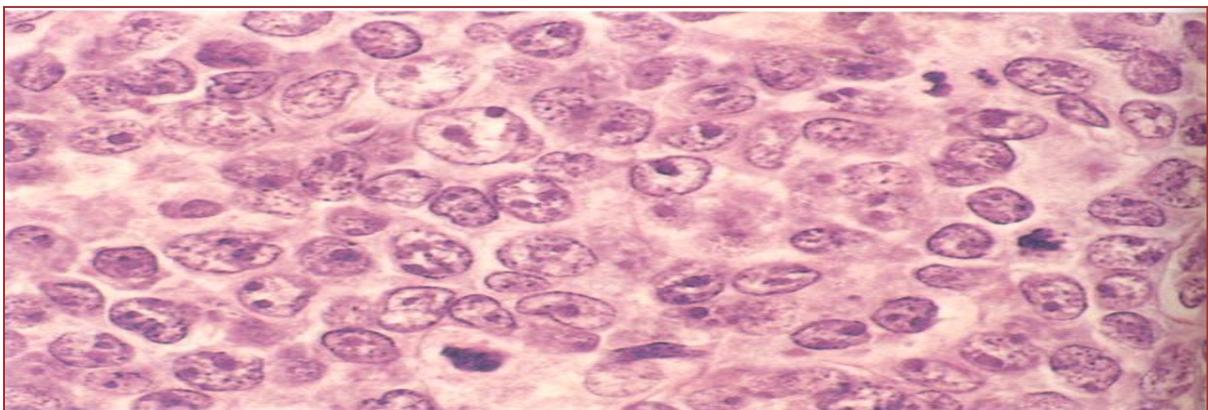
Pneumocystis pneumonia caused by *P. carinii*. A, the alveoli are filled with a characteristic foamy "Cotton candy" exudates. B, silver stain demonstrates cup-shaped cyst walls within the exudates



Cryptococcal infection. A, whole brain section showing the numerous areas of tissue destruction associated with the spread of organism in the pre-vascular spaces. B, at higher magnification it is possible to see the cryptococci in the lesions.



Kaposi sarcoma. A, gross photograph, illustrating coalescent red-purple macules and plaques of the skin. B, Histological view of the nodular form demonstrating sheets of plump, proliferating spindle cells and vascular spaces.



Diffuse large B-cell lymphoma. The tumor cells have large nuclei with open chromatin and prominent nucleoli

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.
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 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**.
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