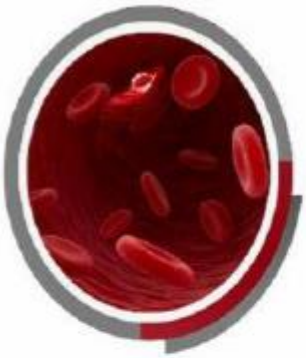

HEMATOLOGY
&LYMPH SYSTEM

Microbiology sheet

Number	2
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Note: information in boxes are copied from the slides, the doctor have read them.

In this lecture we will talk about three viruses (parvovirus,HHV8 and HTLV).

➢ Parvovirus:

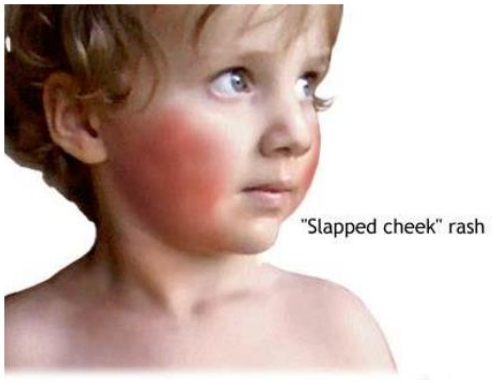
- Parvovirus is a naked single-stranded DNA virus with icosahedral capsid and is the **smallest** among DNA viruses. Most of DNA viruses uncoat in the cytoplasm and replicate their genetic material in the nucleus, but since Parvovirus has a small size, it can enter the nucleus and uncoat there, its replication occurs in the nucleus as well.
- The replication of Parvovirus is unique, it is **totally dependent** on the cellular machinery, it doesn't induce the cell to enter S phase and remain there like other viruses, instead, it **waits** for the cell to enter S phase to replicate its genome and produce new copies of the virus.
- The target cells of Parvovirus are erythroblast (immature, nucleated RBCs); therefore, anemia is one of the consequences of Parvovirus infection.
- Infection with Parvovirus is more common in children, most of the infections are asymptomatic, but some children develop a symptom called *Erythema infectiosum* (also called Slapped Cheek Disease).So if the infected child is healthy and is not showing any symptoms, the infection will pass unnoticed, and a very minimal anemia (if at all) will develop and won't be diagnosed.
- Some patients might develop fever, they are treated with antipyretics, then fever will subside after 3-5 days, and no other sign of infection can be detected.
- The infection is more evidence and problematic in patients who have abnormalities in their RBCs e.g. sickle cell disease or thalassemia, in these cases the infection with Parvovirus will cause **aplastic crisis** or increase the severity of anemia. If an immunosuppressed patient

(e.g. AIDS) suddenly develops bone marrow failure, you should think of Parvovirus as a cause.

- The receptor for Parvovirus is a **P antigen globoside** found on erythroid progenitors, erythroblasts, megakaryocytes and endothelial cells
- The virus can be cultured in bone marrow cells and fetal liver cells
- Parvovirus has three capsid proteins; VP1, VP2, VP3
- Primary site of replication is the nucleus of immature cell in the erythrocyte lineage.

- Incubation period is 4-21 days
- Characterized by fever, malaise, headache, myalgia and itching. Note that these symptoms are nonspecific
- In some cases, lymph nodes are enlarged, and hepatosplenomegaly might develop as well.

- Parvovirus has a distinctive symptom in children which is the **indurated** rash; it appears on the cheeks then spreads to arms and legs in 1-2 days. The illness caused by Parvovirus (nonspecific symptoms and rash) lasts for 1-2 weeks then ceases, but the rash might **recur** in the next 2-4 weeks, rash recurrence is associated with exposure to heat or sun light, exercise, emotional stress or anything that can cause drop in the immunity.



Indurated rash has wavy architecture similar to that of wool

Note: the recurrence of rash is not caused by latency, **there is no latency in Parvovirus infection**, it is an acute lytic infection. What happens is that the immune system doesn't clear the virus completely from the body, so when the immunity drops the remaining viral copies cause rash recurrence.

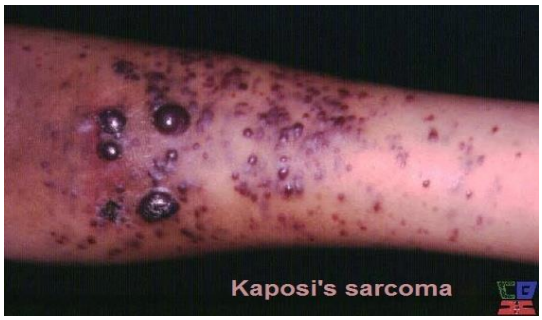
- Transmitted through respiratory route by aerosols or droplets
- More common in Spring months
- It can reach the blood causing viremia that lasts 7-12 days
- Sometimes Parvovirus infection is associated with arthritis and vasculitis
- Rare complications: hepatitis, Thrombocytopenia, nephritis and encephalitis

- Diagnosis is done by PCR or serology looking for IgM antibodies against Parvovirus. Most of the patients are given symptomatic treatments, but in some cases, an immunoglobulin for Parvovirus is given intravenously. These immunoglobulins are very expensive, and they are not a part of the routine treatment of patients with Parvovirus, instead they are preserved for the severely immunosuppressed patients.

➢ Human Herpes Virus 8:

- It belongs to **Gamma**herpesviruses* subfamily (same as EBV virus).
- Originally, the virus was isolated from Kaposi's sarcoma, Kaposi's sarcoma is a skin tumor found in AIDS patients (those in the terminal stage of HIV infection, when all latent viruses reactivate), therefore HHV-8 is called **Kaposi's sarcoma associated herpesvirus (KSHV)**, and it's found in almost 100% of the cases of Kaposi's sarcoma.

- HHV-8 has a very low seroprevalence, meaning that very few people will be found to have antibodies against HHV-8, unlike other viruses which have 90-95% seroprevalence in adults (Remember: the presence of antibodies doesn't necessarily mean that these people got sick or symptomatic).



The above picture show Kaposi's sarcoma..... superficial lesions characterized by dark bluish to black lesions on the skin.

The mechanisms by which the virus is contracted are not well understood:

- Healthy individuals can be infected with the virus and show no signs or symptoms
- Infection is of particular concern to the immunosuppressed. Cancer patients receiving chemotherapy, AIDS patients and organ transplant patients are all at a high risk of showing signs of infection

• *Three subfamilies: (the doctor didn't mention them)

– Alphaherpesviruses - HSV-1, HSV-2, VZV

– Betaherpesviruses - CMV, HHV-6, HHV-7

– Gammaherpesviruses - EBV, HHV-8

- HHV-8 is transmitted by saliva and is more prevalent among groups of individuals susceptible to Kaposi's sarcoma such as homosexuals. In these individuals, the seroprevalence is higher.

To prevent and treat HHV-8 infections we target HIV so:

- Prevention by safe sex and avoidance of high-risk behavior and saliva.
- Treatment by HAART (highly active anti-retroviral therapy), to decrease the load of HIV so that the immune system is able to control and prevent any reactivation of latent viruses.
- Ganciclovir is also used for treatment, but it is not effective if the tumor has already developed.

➢ Human T-cell lymphotropic virus (HTLV):

- Belongs to Retroviridae family of viruses, the family to which HIV belongs, therefore these two viruses are very similar. Note: **Retro**viridae includes HIV and HTLV, whereas **Reo**viridae is the family that includes Rotavirus.
- Revision about HIV (supposing that you have studied this a year ago):

  - HIV targets CD4+ cells (T cells), it has a glycoprotein** (GP120) that binds to CD4 receptors on T cells aided by two co-receptors on the cell (CCR5 or CXCR4), HIV also has a transmembrane glycoprotein (GP41) that makes the membranes of the cell and virus get closer to each other and fuse, making a small hole in the membrane which enlarge allowing the nucleocapsid of the virus to enter the cytoplasm.
  - In the next step, the virus uncoats and releases its genetic material in the cytoplasm. HIV is a (+)sense ssRNA and it is diploid; meaning it has two copies of the genome.
  - Then the viral enzyme reverse transcriptase comes to action, it is a multi-component enzyme. The first component (which is DNA polymerase-like) attaches to the (+)sense strand and complements it with DNA nucleotides (RNA>DNA, the opposite

of transcription), producing an RNA-DNA intermediate. After that, the (+)sense RNA is going to dissociate from the DNA strand ((-)sense), and is destroyed by the enzyme RNAse H (which is another component of the reverse transcriptase enzyme).

- The DNA polymerase-like component of reverse transcriptase acts again to make the single-stranded DNA a double-stranded one. This dsDNA travels from the cytoplasm to the nucleus, where it is going to be incorporated into the cellular genome by the viral enzyme integrase. This enzyme acts on both viral and cellar genomes, where it cuts a few bases from the end of each genome, producing sticky ends so that they can be combined together. Once the viral genome has been incorporated into the cellular genome it is called a provirus.

- The viral genome is then transcribed with the cellular genome by the cellular replication machinery, producing mRNA ((+) sense), which exits the nucleus to go to the cytoplasm where it can be either translated into proteins (a polyprotein is produced first and cleaved after a while by a protease enzyme) or packed with the newly formed copies of the virus as a genome (two (+)sense copies for each virus) followed by assembly and release of the virus.

All the information mentioned above about HIV also applies for HTLV.

- HTLV is characterized by a long incubation period, even longer than that of HIV, the virus might take 20-40 years to produce a disease **UNLESS** an immunosuppressive condition happens, which decreases incubation period.
- Most of the patients infected with HTLV don't know that they are infected, and minority (2-5%) might develop cancer after this long incubation period.
- The latency of HTLV (and HIV) is called **clinical latency**, here the virus is present in the body and can be detected, and it is fighting against the immune system in a continuous and fluctuating manner.
- *Two types* of HTLV exist; HTLV-I and HTLV-II, each of them causes specific set of diseases.

HTLV-I is associated with 2 fatal human diseases:

- Adult T cell leukemia (ATL): clonal malignancy of infected mature CD4+ T cells
- Tropical spastic paraparesis/HTLV-1 associated myelopathy : neurodegenerative disease

Endemic in parts of Japan, South America, Africa, Caribbean and Iran, with an estimated 10-20 million people infected worldwide.

transmission and only 1% female to male), unlike HIV infection which is common among male homosexuals

- Vertical: during breast feeding, 20% of children from infected mothers acquire the virus
- Blood products
- Extended close contact (cell-associated virus)
- Between IV drug abusers

Note: Transmission through breast feeding is implicated as a major route for the maintenance of infection prevalence in areas of high endemicity; meaning that it keeps the percentage of infections stable.

Pathogenesis:

- Adult T-cell lymphoma/leukemia (ATL) is associated with HTLV-I infection of the tumor clone in 100 percent of cases.
- In all malignant cells in an affected individual, the **HTLV-I pro-viral genome** is incorporated into an identical location of the genome.
- The long-term risk of developing ATL following infection with HTLV-I in endemic areas has been estimated to be 4 to 5 percent, usually after a latency period of several decades.
- Exposure to the virus early in life increases the risk of eventual development of ATL.
- A shorter latency period has been noted in infected patients receiving treatment with immunosuppressive agents for other reasons.

The exact mechanism by which HTLV-I contributes to tumor development is unknown. However, increasing evidence suggests that the viral regulatory gene TAX (transactivating gene of the X region) encodes an oncoprotein, named TAX protein.

TAX protein induces **cellular proliferation, promotes cellular survival, and impairs DNA damage repair mechanisms.**

The organs involved vary but can include the peripheral blood and bone marrow, lymph nodes, and skin. The **most characteristic morphologic change** seen in ATL is in the peripheral blood of leukemic cases. In such cases, medium sized lymphocytes with condensed chromatin and bizarre hyperlobated nuclei ("clover leaf" or "flower cells") can be found. Bone marrow involvement is seen in approximately 35 percent of cases. **Bone marrow infiltrates are usually patchy, ranging from sparse to moderate**.

- Diagnosis of HTLV is also similar to that of HIV: **screening by ELISA and confirmation by Western blotting and PCR**. A definite diagnosis of ATL is made by documenting the presence of HTLV-I proviral DNA in the DNA of tumor cells.
- In general, **PCR** is the best if you are looking for viral genetic material in the cell (important is assessing viral load), while Western blotting is the best if you are looking for viral parts (proteins).

HTLV-I is also associated with a progressive demyelinating upper motor neuron disease known as HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP), and characterized by sensory and motor deficits, particularly of the lower extremities, incontinence and impotence.

HTLV-II is associated with Hairy cell leukemia; a rare lymphocytic leukemia of B cell origin, it is characterized by malignant cells that look **ciliated.**

Treatment:
The long incubation period and the continuous battle between the virus and the immune system might give a chance for opportunistic infections to occur, therefore, careful observation to aggressive chemotherapy should be done and antiretroviral agents should be given.
Adult T cell lymphoma is treated with chemotherapy and interferon.
HTLV myelopathy is treated with corticosteroids ,to reduce the inflammation, and interferon, to aid the immune system, (symptomatic treatment).

**HIV contain a glycoprotein called gp160 which is composed of two subunits (gp120 and gp41). The gp41 is the transmembrane subunit (part of it is imbedded in the envelop). The gp120 is the most outer partof the glycoprotein.

Thank you