Virology

Lec (9)

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Human herpesvirus 6 (HHV-6) is the common collective name for human herpesvirus 6A (HHV-6A) and human herpesvirus 6B (HHV-6B). These closely related viruses are two of the nine herpesviruses known to have humans as their primary host.

HHV-6A and HHV-6B are double stranded DNA viruses within the betaherpesvirinae subfamily and of the genus Roseolovirus. HHV-6A and HHV-6B infect almost all of the human populations that have been tested.

HHV-6A has been described as more neurovirulent, and as such is more frequently found in patients with neuro-inflammatory diseases such as multiple sclerosis; HHV-6 and HHV-7, levels in the brain are also elevated in people with Alzheimer's disease.

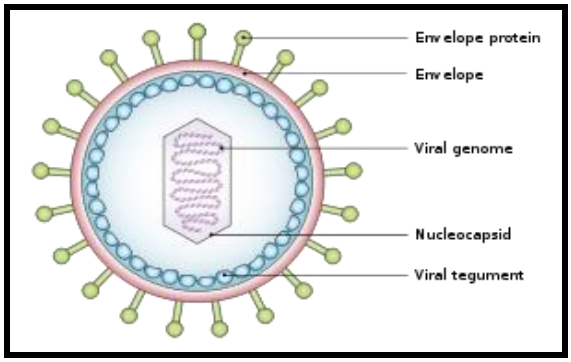
HHV-6B primary infection is the cause of the common childhood illness exanthema subitum (also known as roseola infantum or sixth disease). Additionally, HHV-6B reactivation is common in transplant recipients, which can cause several clinical manifestations such as encephalitis, bone marrow suppression, and pneumonitis. A variety of tests are used in the detection HHV-6, some of which do not differentiate the two species.

Epstein-Barr virus (EBV) or Human herpesvirus 4.

Is a gammaherpesvirus that infects more than 95% of the world's population. It is best known as the cause of infectious mononucleosis (glandular fever). It is also associated with particular forms of cancer, such as Hodgkin's lymphoma, Burkitt's lymphoma, nasopharyngeal carcinoma, and conditions associated with human immunodeficiency virus (HIV), such as hairy leukoplakia and central nervous system lymphomas.

Important Properties of EBV.

- Epstein-Barr virus is structurally and morphologically identical to other herpisviruses but is antigenically different. It has a two serotype depend on **nuclear antigen (EBNA), and (EBER).**
- The virus is approximately 122 - 180 nm in diameter and is composed of a double helix of DNA and is surrounded by a protein nucleocapsid. This nucleocapsid is surrounded by a tegument made of protein, which in turn is surrounded by an envelope containing both lipids and surface projections of glycoproteins which are essential to infection of the host cell.



Transmission

- Epstein-Barr virus is transmitted via saliva through speaking, kissing and sexual contact, hence the name 'kissing disease'. Infection is common in younger children and sexually active adolescents.
- Blood transmission is very rare.

Summary of replicative cycle

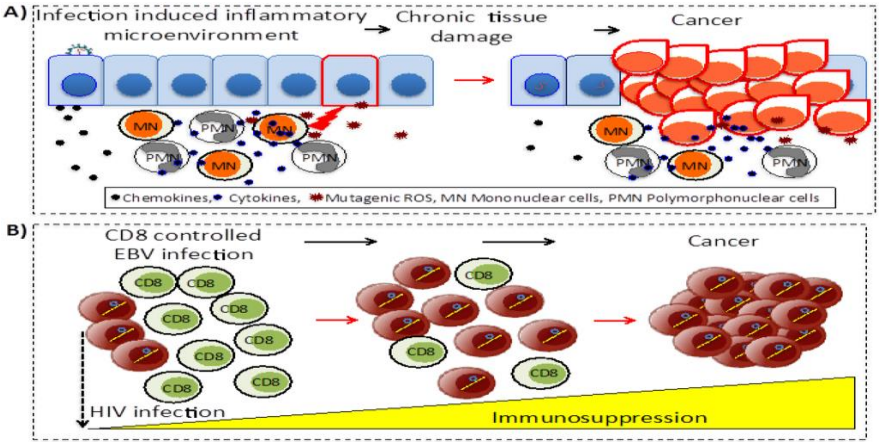
- The cycle is similar to that of HSV, but EBV can infect different cell types, including B cells and epithelial cells.
- Epstein-Barr virus enters B lymphocytes at the site of the receptor for the component of complement (CR2) or CD21.
- The viral three-part glycoprotein complexes of **gH gL gp42** mediate B cell membrane fusion; although the two-part complexes of **gH gL** mediate epithelial cell membrane fusion. EBV that are made in the B cells have low numbers of **gHgLgp42** complexes, because these three-part complexes interact with Human-leukocyte-antigen class II molecules present in B cells in the endoplasmic reticulum and are degraded. In contrast, EBV from epithelial cells are rich in the three-part complexes because these cells do not normally contain HLA class II molecules. As a consequence, EBV made from B cells is more infectious to epithelial cells, and EBV made from epithelial cells are more infectious to B cells. Viruses lacking the gp42 portion are able to bind to human B cells but unable to infect.
- The EBV genome becomes circular, forming an episome in B cell and remains latent in these cells, during primary infection viral expressed six nuclear antigens (EBNA-1,-2,-3A, -3B, -3C and leader protein, and three integral membrane proteins(LMP-1, LMP-2A and -2B), as well as two small EBV encoded RNAs (EBER1 and EBER-2).

Pathogenesis

The infection first occurs in the oropharynx, when viral replication occurs in epithelial cells of the pharynx and salivary gland. And then spreads to the blood, where it infects B lymphocytes.

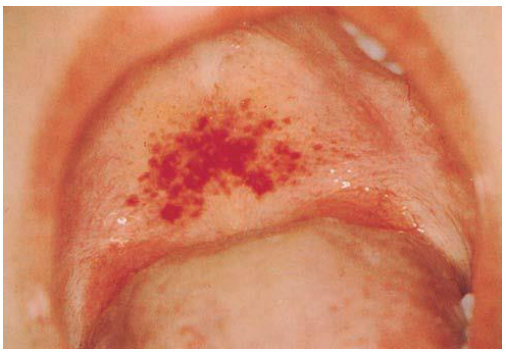
Cytotoxic T lymphocytes react against the infected B cell, EBV remains latent within B lymphocytes.

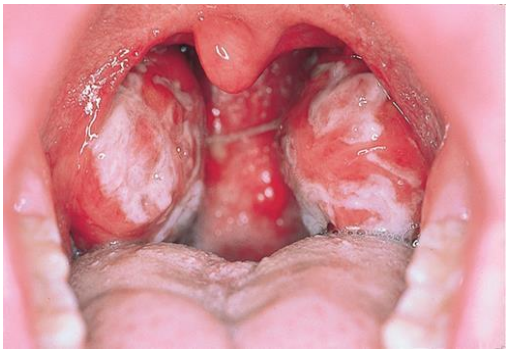
The immune response to EBV infection consist first of IgM antibody to the viral capside antigen, IgG antibody to the viral capside antigen follows and persists for life. In addition to the EBV-specific antibodies, nonspecific heterophial antibodies are found, the term heterophil refer to antibodies that are detected by tests using antigens different from the antigens that induced them.
Reactivation of EBV latent infection can occur but are usually asymptomatic. Immunosuppresion is a factor of reactivation infection.



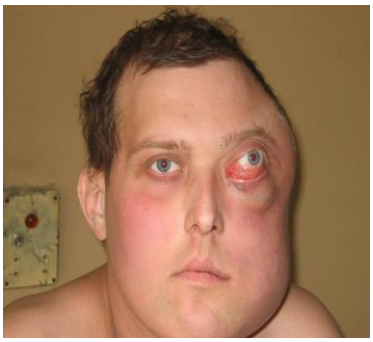
Clinical findings

1- Infectious mononucleosis infections occur in children, and usually asymptomatic. In older children and adults is characterized by sore throat, fever, anorexia, lymphoadenopathy and splenomegaly. Hepatitis and encephalitis occurs in some patients. Spontaneous recovery usually occurs in 2-3 weeks. 90% of cases IM are due to EBV and 5-10% of cases are due to cytomegalovirus less common causes rubella, HIV, Hepatitis viruses and Toxoplasma

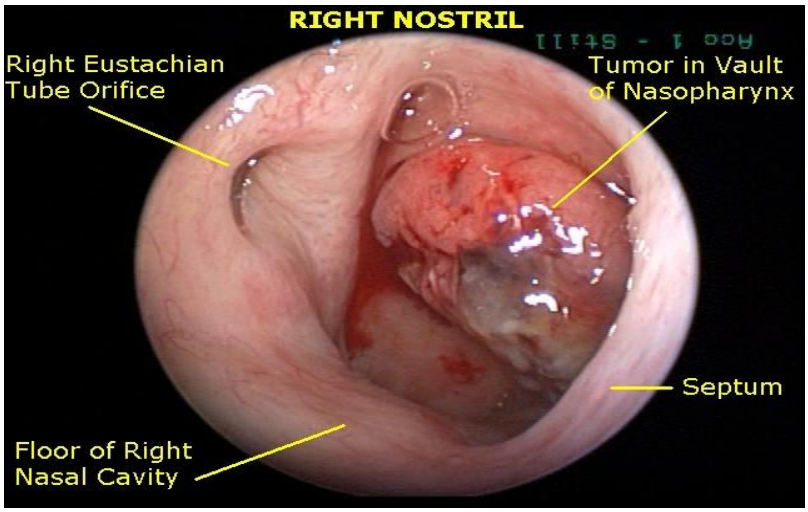




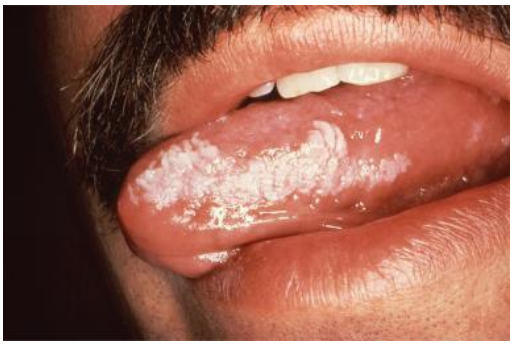
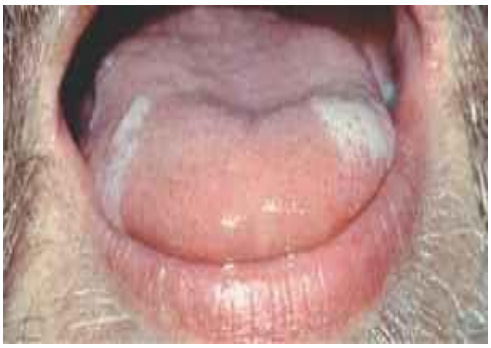
2- Burkitt's lymphoma, EBV is associated with over 90% of cases of Burkitt's lymphoma (a huge tumor mass of the jaw bone in African children and young adults). It responds quickly to chemotherapy treatment.



3- Nasopharyngeal carcinoma is a cancer of epithelial cells is common in males of Chinese origin. Which raises the possibility of viral oncogenesis on a background of genetic susceptibility.



4- Oral hairy leukoplakia is a wort-like growth develop on the tongue of some HIV infected patients and transplant patients.

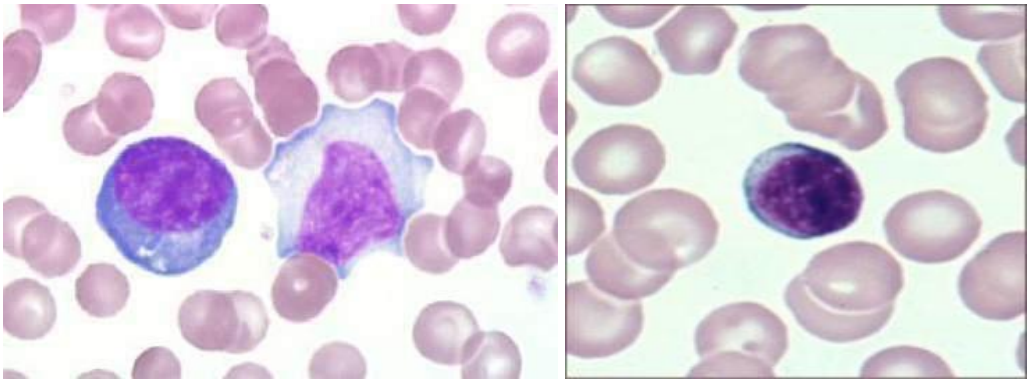



5- EBV is recognized as the cause of Hodgkin's disease and Non- Hodgkin's disease in patients with HIV

Laboratory diagnosis

1- Hematologic tests

- Approach 30% abnormal lymphocytes are seen on a blood smear.
- Specific heterophil agglutination test may be used for diagnosis of EBV-infection.



2- **Serological test**

- The common serological procedure is ELISA. Early in acute disease, a rise in IgM to viral capsid antigen (VCA) replaced within weeks by IgG which persist for life. The presence of anti-VCA IgM suggestive of recent infection, while the presence of anti-VCA IgG indicate past infection and immunity.
- EBV nuclear antigen (EBNA) antibody. This antibody is produced about 3 months after infection. If positive, it indicates EBV infection more than 3 months ago.
- EBNA antibody negative, VCA antibody positive. Suggests recent EBV infection but beware of false negative EBNA results, especially in patients >60 years old and immune suppressed patients.

3- **Molecular assays**

- The presence of EBV DNA indicates current infection. Quantitative PCR is a guide to the severity of infection in immune compromised patients and a guide to management.

Treatment and prevention.

-There is no EBV vaccine.

-No antiviral therapy is necessary for uncomplicated infectious mononucleosis. Acyclovir has little activity against EBV.

- You can help protect yourself by not kissing or sharing drinks, food, or personal items, like toothbrushes, with people who have EBV infection.

Human herpesvirus type 8 or Kaposi's sarcoma associated herpesvirus (KSHV)

-It was first detected in 1994. it was reported that a new herpesvirus, now known as HHV-8, Kaposi's sarcoma associated herpesvirus (KSHV).

- Transmission of HHV-8 is primarily sexually, but it is also transmitted in transplanted organs such as kidneys and appears to be the cause of transplantation-associated KS.

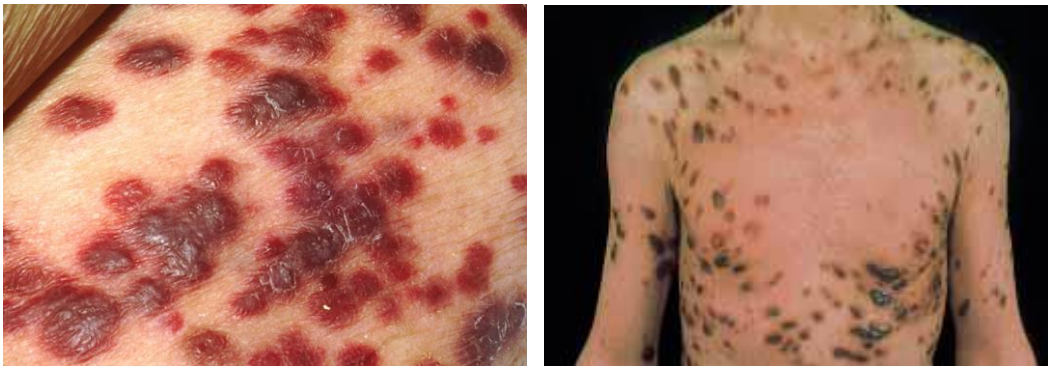
-The most common cancer in patients with AIDS. Epidemiologic data that showed that KSHV was common in patients who acquired HIV sexually but rare in patients who acquired HIV via blood transfusion.

-HHV-8 causes malignant transformation by a mechanism similar to that of other DNA viruses (such as human papillomavirus), namely, inactivation of a tumor suppressor gene. A protein encoded by HHV-8 called nuclear antigen inactivates the RB (retinoblastoma) tumor suppressor protein, which causes the cells to grow in an uncontrolled manner.

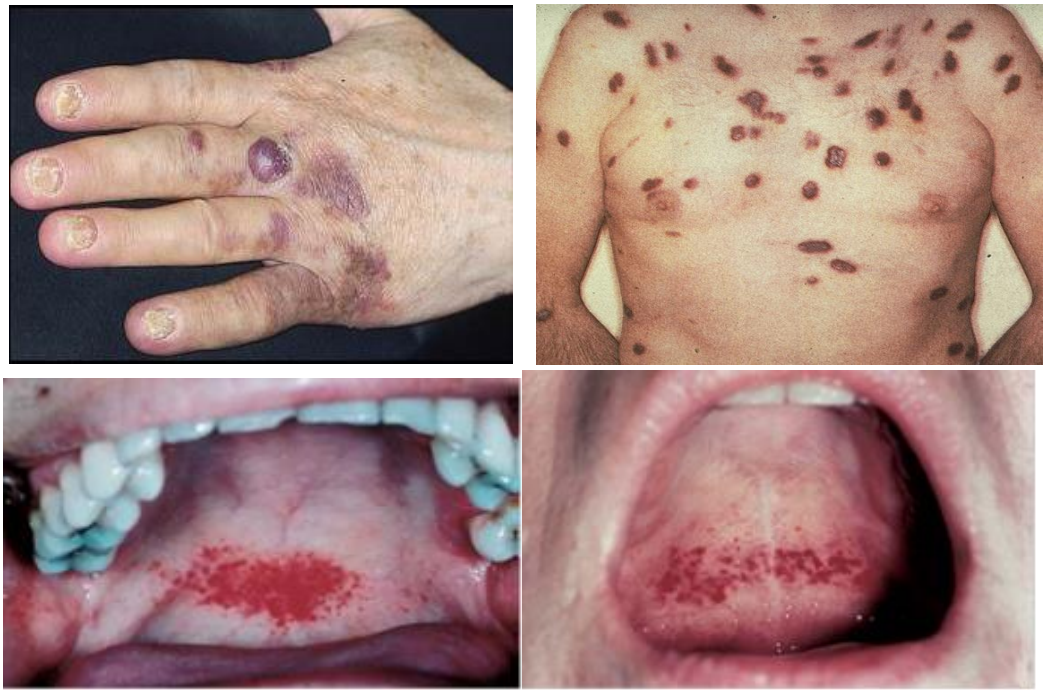
-**KS in AIDS patients** is a malignancy of vascular endothelial cells that contains many spindle-shaped cells and erythrocytes. The lesions are dark purple, flat to nodular, and often appear at multiple sites such as the skin, oral cavity, and soles (but not the palms). Internally, lesions occur commonly in the gastrointestinal tract and the lungs. The extravasated red cells give the lesions their purplish color. HHV-8 also infects B cells, inducing them to proliferate and produce a type of lymphoma called primary effusion lymphoma.

-**Laboratory diagnosis** of KS is often made by biopsy of the skin lesions. HHV-8 DNA and RNA are present in most spindle cells, but that analysis is not usually done. Virus is not grown in culture.

-**The type of treatment** depends upon the site and number of the lesions. Surgical excision, radiation, and systemic drugs, such as alpha interferon or vinblastine, can be used. There is no specific antiviral therapy and no vaccine against HHV-8.



Kaposi's sarcoma



Infectious mononucleosis. Petechial hemorrhages of the soft palate and oral pharynx, in conjunction with constitutional symptoms of low-grade fever, malaise, and cervical lymphadenopathy are characteristic of infectious mononucleosis.