Hematology

MICROBIOLOGY

☑ Sheet ☐ Slide ☐ Handout

Number: **1**

Subject: **Epstein-Barr virus**

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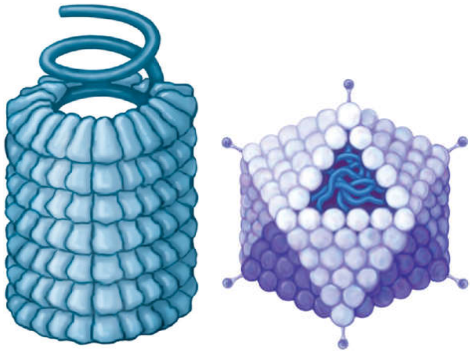
Price:

بسم الله الرحمن الرحيم

Herpes Simplex Viridae Family:

- They are dsDNA, linear, enveloped viruses
- There's 50-70% similarity between them
- Cross reactivity can occur between HSV and VZV
- The dsDNA is surrounded by capsid, the capsid are of two types:
  a) Icosahedral b) Helical
- The capsid is surrounded by a tegument which contains viral proteins, and the tegument is surrounded by an envelope.



The herpes simplex family consist of 8 members:

- HSV1
- HSV2
- HSV3 or Varicella Zoster Virus VZV
- HSV4 or Epstein Bar Virus
- HSV5 or Cytomegalovirus CMV
- HSV6
- HSV7
- HSV8 (Kaposi Sarcoma associated virus)

α: 1,2,3 **β**:5,6,7 **γ**:4,8

What's Unique about HSV family?

- *It has a latency period*

These viruses become latent by becoming

1) Extra chromosomal circular double stranded DNA *"a state called an **Episome**"*
2) Or by producing the immediate early proteins of the virus or minority of these proteins

When there is latency there is no incorporation or integration of the viral genome to the cell genome

When the virus is in latency period:

1. It cannot respond to treatment with antiviral drugs
2. It cannot be detected by blood tests

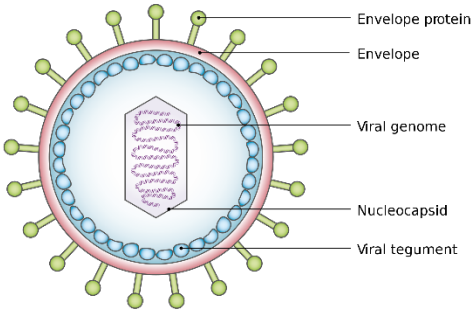
To make it easy to memorize the families of viruses we put all the DNA viruses into one phrase:
1A, 3H, 3P

The **1A** stands for: **A**denoviruses.

The **3H** stands for: **H**erpes simplex viruses, **H**epatitis b, **H**uman papilloma virus.

The **3P** stands for: **P**olyomaviridae, **P**arvoviridae, **P**oxviridae.

Epstein Bar Virus (EBV):



- A virus of the herpes viridae family, and gamma herpes viruses subfamily, genome codes for 100-200 proteins but only few have been identified .
- Icosahedral capsid, infection occurs worldwide.
- The viral genome does not normally integrate into the cellular DNA.
- Two strains A and B. cell receptors are CR2 and CD21 on b cells.
- It's able to establish a long term latent infection in B-cells.
- Acute infection followed by latent infection, in the latent period the virus genome present as an Episome, not integrated.
- Reactivation gives recurrent disease when drop of immunity occurs *"like AIDS or immunosuprresive therapy".*
- Membrane is derived by budding of immature particles through cell membrane and is required for infectivity.
- Immediate early proteins are what initiate and regulate transcription.
- Early proteins are non-structural proteins (DNA polymerase, and Thymidine Kinase).
- Late proteins are major structural proteins (capsids, spikes).
- Tissue tropism: memory B-cells and epithelial cells of Oropharynx.
- Latency: Memory B-cells.

Diseases associated with EBV:

In B cells:

Infectious mononucleosis, Hodgkin's disease, Burkitt lymphoma

In other cells:

Nasopharyngeal carcinoma, gastric carcinoma, oral hairy leukoplakia

"As well as several AIDS related cancers, most prominently diffuse large B Cell Lymphoma DLBCL"

Infection rates:

In the developed countries:

50% of children under 5 have seroconversion (previous exposure to the virus)

90% between the ages of 18-20 have seroconversion

In the developing countries:

90% of children under 5 have seroconcersion

"It's related to personal hygiene"

Primary routes of infection:

I. Saliva (i.e. kissing)
II. Blood products and bone marrow transplant

- Its infection has another name among teenager called “kissing disease” due to its transmission through the saliva or it can be called Infectious mononucleosis, a disease of young adulthood.
- It can also be transmitted to the children via kissing or by the mother when she chews the food for her baby.
- These infections are most common in early childhood, with a second peak during late adolescence.
- By adulthood, more than 90% of individuals have been infected and have antibodies to the virus.
- Transmission may occur through fomites “personal belongings” contaminated with wet saliva.
- Cellular immunity is more important than humoral immunity in controlling EBV infection because the virus is intracellular, If T cell immunity is compromised, EBV-infected B cells may begin to proliferate “*Reactivation*”.
- EBV is able to immortalize B-lymphocytes in vitro and in vivo, in favor of the virus replication.

Infectious Mononucleosis (IM):

- Symptoms: fatigue, malaise, low-grade fever and lymphadenopathy and pharyngitis in first two weeks, could be associated with hepatomegaly and splenomegaly in the 2nd and 3rd week.
- Incubation period in young adults is 4 to 6 weeks.

  - Lab Findings:

    - The WBC count is usually elevated and peaks at 10,000 to 20,000/L during the second or third week of illness.
    - Lymphocytosis is usually demonstrable, with >10% atypical lymphocytes (CD8 predominantly).
    - Low-grade neutropenia and thrombocytopenia.
    - Liver function is abnormal in more than 90% of cases, and the liver enzymes are elevated.
    - Heterophile antibody titers rise during the first two weeks, 60-90% in the second or third weeks.

- The level of antibody gradually declines and usually disappears in eight to twelve weeks following the onset, Elevated titers sometimes linger for four to six months up to a year or more especially the (D) antigen, and 20% of cases may remain for a lifetime.
- Heterophile antibody most commonly used in the serological diagnosis of IM

Time course of antibody production:

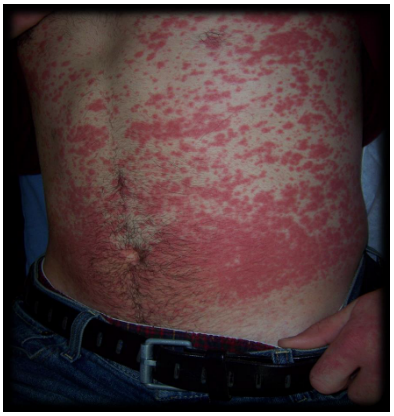
- EA rise for 3-4 weeks
- VCA-IgM peaks at 2-3 weeks
- VCA-IgG peaks at 2-3 months
- EBNA: convalescence and remain present for life (indication of previous infection)

MAIN CAUSES OF EXUDATIVE PHARYNGITIS
90% IS STREPTOCOCCAL PYOGENS
10% EBV, CMV, ADENOVIRUS
SO MAINLY WE TREAT IT WITH ANTIBIOTICS
BUT IF THERE WAS AN EXAGGERATION OF SKIN RASH WHILE TREATING WITH ANTIBIOTIC THENTHIS INDICATES THAT PATIENT HAVE "**IM**" AND WE SHOULD TREAT HIM WITH ANTIVIRAL DRUG INSTEAD

Primary infection of EBV in young adults or teenagers gives IM "kissing disease"

- Patients are banned from strenuous exercise to avoid ruptured spleen and internal bleeding that may lead to death, because the spleen is enlarged.
- Lymphadenopathy most often affects the posterior cervical nodes but may affect other head and neck lymph nodes.

Pharyngitis, often the most prominent sign, can be accompanied by enlargement of the tonsils with an exudate resembling that of streptococcal pharyngitis



- A morbilliform or papular rash, usually on the arms or trunk, develops in 5% of cases
- Most patients treated with ampicillin develop a macular rash

IM treatment:

- Supportive measures, with rest and analgesia. (self-limited illness)
- Excessive physical activity during the first month should be avoided to reduce the possibility of splenic rupture like we said
- Acyclovir can be taken to help with the treatment
- And if he's on medication that leads to immunosuppression the dose should be reduced to alleviate the immunosuppression state to get out of the acute stage of the illness
- Also we can give : Interferon, antibody to CD20, Infusions of EBVspecific cytotoxic T cells

The isolation of patients with IM is unnecessary

Burkitt's lymphoma (BL):

- Occurs endemically in parts of Africa, it's the commonest childhood tumor
- It usually occurs in children aged 3-14 years
- It respond favorably to chemotherapy
- It is restricted to areas with holoendemic malaria, therefore it appears that malaria infection is a cofactor
- It infects the Bone marrow specially in the jaw, which results in enlarged jaw bones and leads to dysmorphic figure of the patient.
  ultiple copies of EBV genome and some EBV antigens can be found in BL cells and patients with BL have high titres of antibodi es against various EBV antigen.

EBV+:

- 90% of cases in developing countries – jaw tumors
- 20% cases in US – children with abdominal tumors
- AIDS patients – tumors in lymph nodes

All are treated with Chemotherapy

B-cell Lymphoma (DLBCL):

- In most individuals infected with EBV, the virus is present in the B-cells, which are normally controlled by T-lymphocytes
- When T-cell deficiency exists, one clone of EBV-infected B-lymphocytes escapes immune surveillance to become autonomously proliferating
- EBV induced B cell lymphomas are most prevalent in immunocompromised patients

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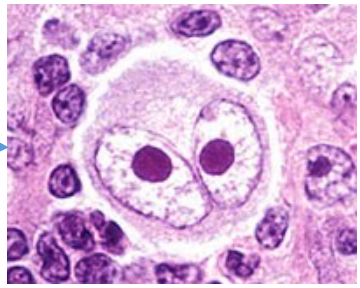
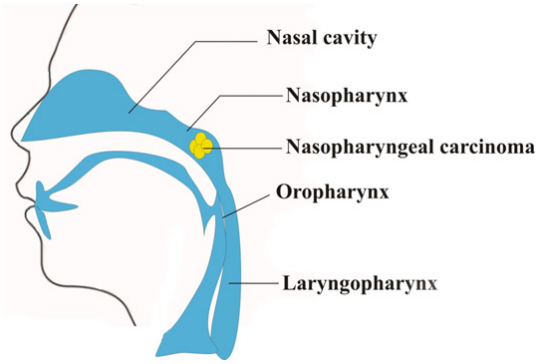
Hodgkin's disease:

- EBV+ in 60-70% of cases in developing countries
- And 35-50% cases in US
- EBV exists in Reed-Sternberg cells
- Therapy: Chemotherapy, radiation Anti-EBV CTLs effective in some cases



Nasopharyngeal Carcinoma NPC



- A malignant tumor of the squamous epithelium of the nasopharynx
- It is very prevalent in S. China, where it is the commonest tumor in men and the second commonest in women (because they eat raw smoked fish which's high in nitrous amide, a carcinogenic substance)
- Multiple copies of EBV genome and EBV EBNA-1 antigen can be found in cells of undifferentiated NPC, patients with NPC have high titers of antibodies against various EBV antigens.
- Besides EBV there appears to be a number of environmental and genetic cofactors in NPC.
- NPC usually presents late and thus the prognosis is poor, theoretically can be prevented by vaccination.

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*In **Immunocompromised** patients reactivation of latent EBV occurs and causes proliferation of the virus and cancer*

Molecular Biology of EBV:

Replication	Latency
Viral capsid antigens (VCAs), IGM or IGG EBV Early antigens (EAs) or (D) antigen EBV Nuclear antigen (EBNA)	Latently infected B cells are the primary reservoir of EBV in the body Only 11 genes are expressed during viral latency

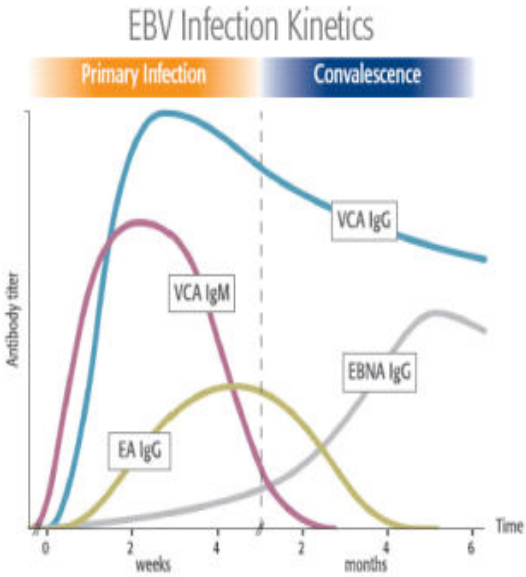
Diagnosis of acute EBV infection is usually made by the heterophile antibody test and/or detection of anti-EBV VCA IgM

Cases of NPC should be diagnosed by histology.

The determination of the titre of anti-EBV VCA IgA in screening for early lesions of NPC and also for monitoring treatment (if the amount is decreasing then the patient is responding to therapy).

Serum Epstein-Barr Virus (EBV) Antibodies in EBV Infection

Infection	VCA IgG	VCA IgM	EA(D)	EBNA
No previous infection	-	-	-	-
Acute infection	+	+	+/-	-
Recent infection	+	+/-	+/-	+/-
Past infection	+	-	+/-	+



- If they are all negative means the patient have never been exposed to the virus and susceptible to it (no immunity against the virus).
- Acute infection: IgG & IgM are positive and the early antigen D could be positive.
- Recent infection: IgG is positive IgM & EA D not necessarily, EBNA depending on the state, if it's late means the nuclear antigen is going to be present, earlier means it's not going to be present
- Past infection: IgG and EBNA are present
- If IgG, EBNA and EA D are present means there is a reactivation of the virus