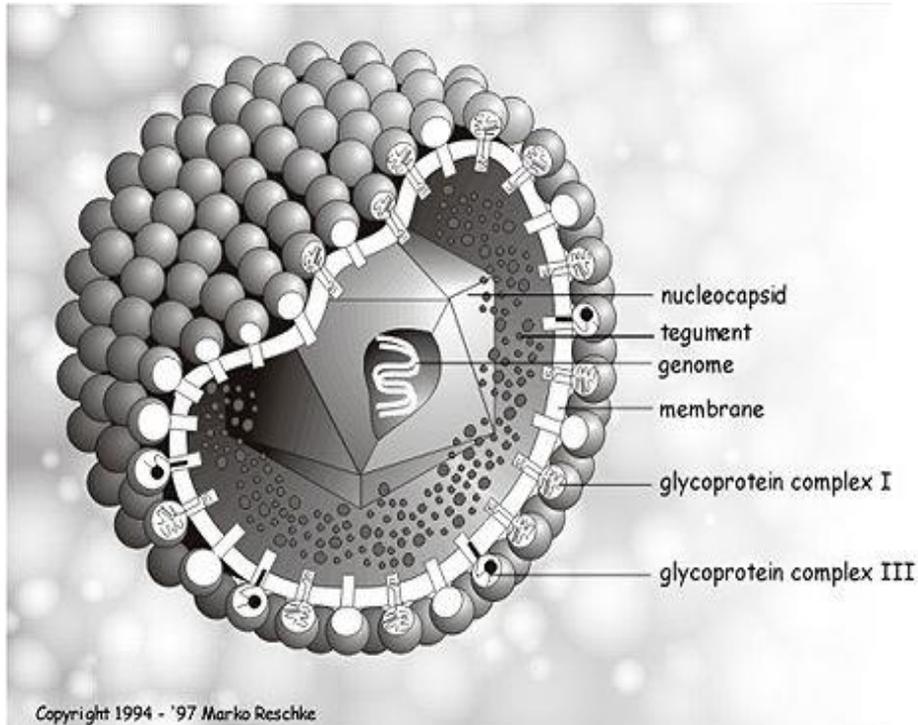


Epstein-Barr Virus

Herpesviruses

- dsDNA , linear, enveloped, 180-200 nm
- Large genome, codes for 75 viral proteins
- 50-70% similarity
- Cross reactivity between HSV and VZV

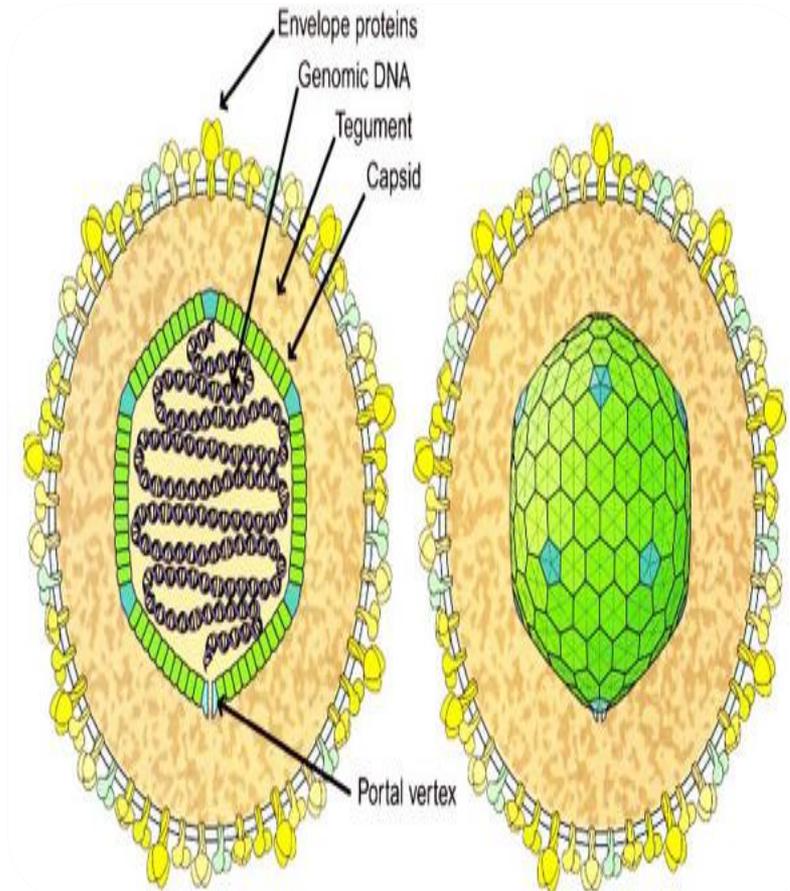


HSV-2 virus particle. Note that all herpesviruses have identical morphology and cannot be distinguished from each other under electron microscopy.

- Three subfamilies:
 - Alphaherpesviruses - HSV-1, HSV-2, VZV
 - Betaherpesviruses - CMV, HHV-6, HHV-7
 - Gammaherpesviruses - EBV, HHV-8
- Acute infection followed by latent infection
- Latent: virus genome present in the cell (episome), not integrated
- Reactivation gives recurrent disease
- Replication: receptor, heparan sulphate
- IE (proteins initiate and regulate transcription)
- E: non-structural proteins (DNA poly., TK)
- L: major structural proteins (capsid, spikes)
- role of TK, polymerase, in antiviral effect.
- Only 25% of DNA/protein produced incorporated into virions

Importance of Epstein barr virus

- **Epstein-Barr virus (EBV) is a human γ -herpesvirus that is able to establish a long-term, latent infection in human B cells for the life of the host. EBV infection is associated with a range of human cancers, including Burkitt's lymphoma (BL) and Hodgkin's disease, as well as several AIDS-associated cancers of which the most prevalent is diffuse large B-cell lymphoma (DLBCL).**



Epidemiology

- EBV infections occur worldwide.
- 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.
- IM is usually a disease of young adults.
- EBV is spread by contact with oral secretions.
- The virus is frequently transmitted from asymptomatic adults to infants and among young adults by transfer of saliva during kissing.
- Transmission by Fomites contaminated with wet saliva is feasible.
- EBV has been transmitted by blood transfusion and by bone marrow transplantation.
- More than 90% of asymptomatic seropositive individuals shed the virus in oropharyngeal secretions.

Diseases Associated with EBV

EBV in B Cell

Infectious mononucleosis

X-Linked Lymphoproliferative Disease

Chronic active EBV

Hodgkin Disease

Burkitt Lymphoma

Lymphoproliferative disease

EBV in Other Cells

Nasopharyngeal carcinoma

Gastric carcinoma

Nasal T/NK cell lymphomas

Peripheral T cell lymphomas

Oral hairy leukoplakia

Smooth muscle tumors in transplant patients

Mononucleosis causes:

- Fever
- Fatigue
- Sore throat
- Swollen lymph glands



Epstein-Barr Virus (EBV)

- Belong to the gammaherpesvirus subfamily of herpes viruses
- Nucleocapsid 100 nm in diameter, with 162 capsomers
- Membrane is derived by budding of immature particles through cell membrane and is required for infectivity.
- Genome is a linear double stranded DNA molecule with 172 kbp
- The viral genome does not normally integrate into the cellular DNA but forms circular episomes which reside in the nucleus.
- The genome is large enough to code for 100 - 200 proteins but only a few have been identified.
- Two strains A and B. cell receptors are CR2 and CD21

Pathogenesis

- EBV is transmitted by salivary secretions.
- The virus infects the epithelium of the **oropharynx** and the salivary glands and is shed from these cells.
- The virus then spreads through the bloodstream.
- Data suggest that **memory B cells**, not epithelial cells, are the reservoir for EBV in the body.
- **Cellular immunity** is more important than humoral immunity in controlling EBV infection.
- If T cell immunity is **compromised**, EBV-infected B cells may begin to proliferate.
- EBV is able to immortalize B-lymphocytes in vitro and in vivo

Disease Association

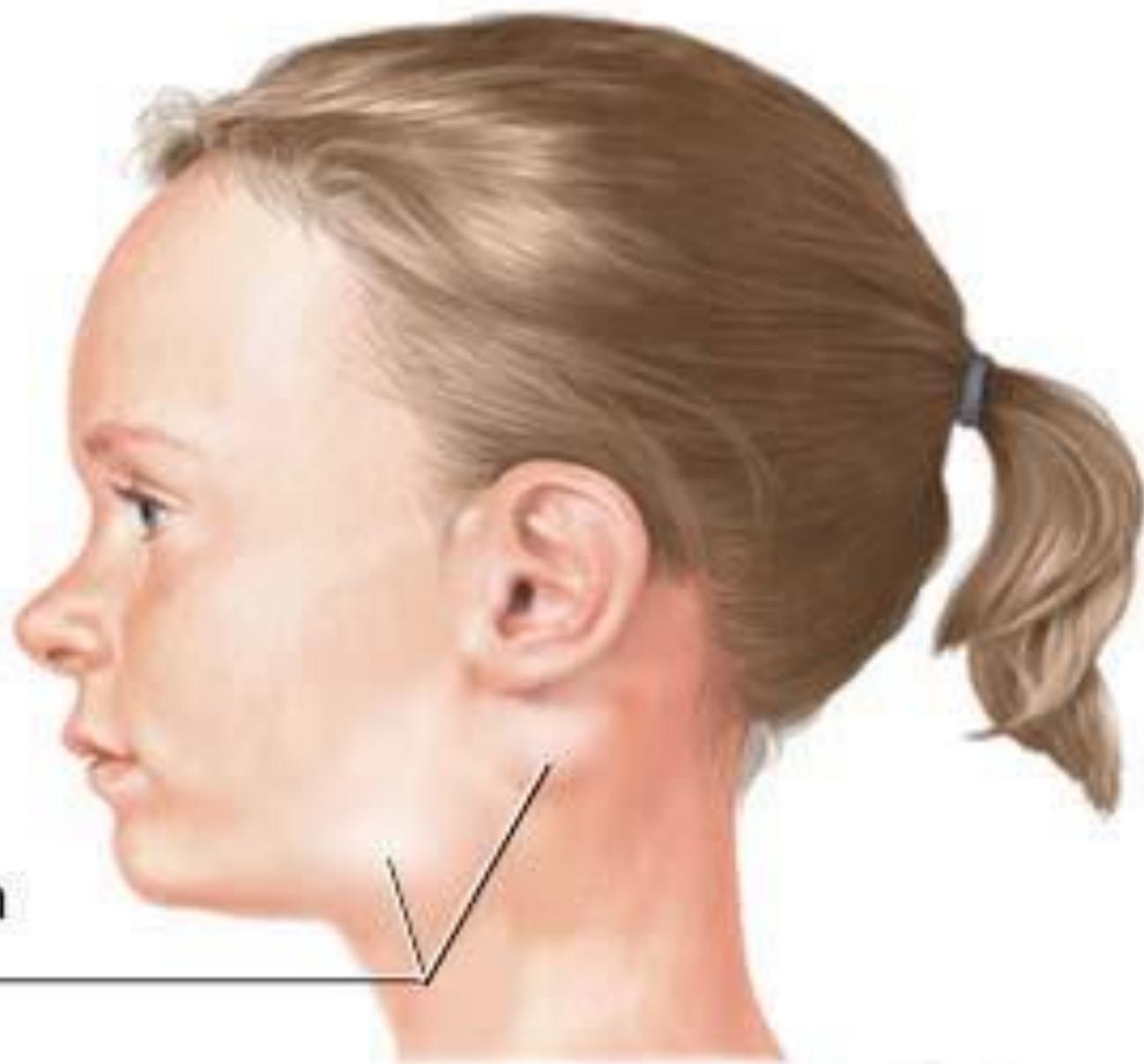
1. Infectious Mononucleosis
2. Burkitt's lymphoma
3. Nasopharyngeal carcinoma
4. Lymphoproliferative disease and lymphoma in the immunosuppressed.
5. X-linked lymphoproliferative syndrome
6. Chronic infectious mononucleosis
7. Oral leukoplakia in AIDS patients
8. Chronic interstitial pneumonitis in AIDS patients.

Infectious Mononucleosis

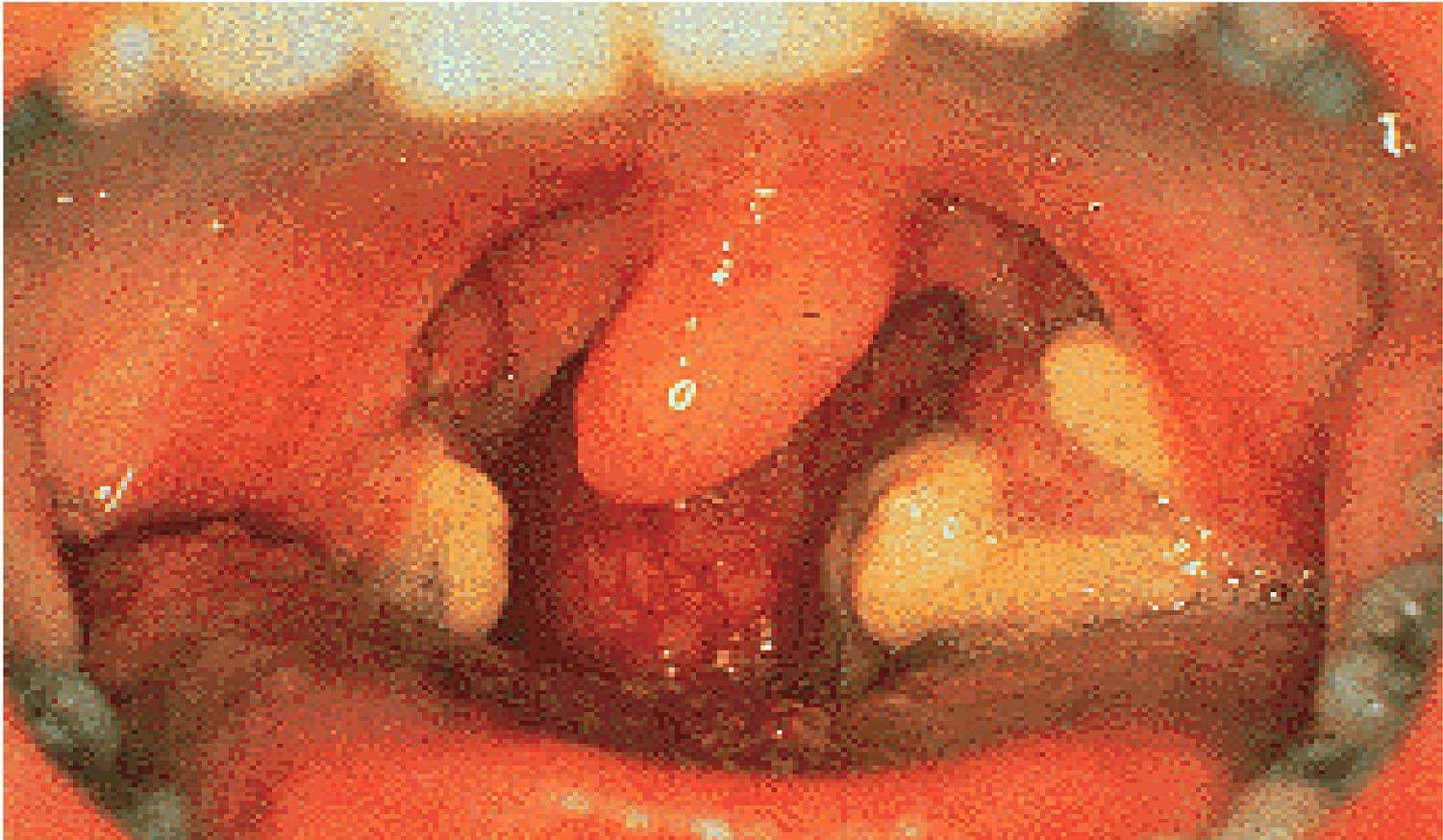
- The incubation period for IM in young adults is 4 to 6 weeks.
- A prodrome of fatigue, malaise, and myalgia may last for 1 to 2 weeks before the onset of fever, sore throat, and lymphadenopathy.
- Fever is usually low-grade and is most common in the first 2 weeks of the illness; however, it may persist **for 1 month**.
- Lymphadenopathy and pharyngitis are most prominent during the first 2 weeks of the illness, while splenomegaly is more prominent during the second and third weeks.
- Lymphadenopathy most often affects the posterior cervical nodes but may be generalized.
- Enlarged lymph nodes are frequently tender and symmetric but are not fixed in place.
-
- 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; this rash is not predictive of future adverse reactions to penicillins.

Mononucleosis causes:

- Fever
- Fatigue
- Sore throat
- Swollen lymph glands



Infectious Mononucleosis

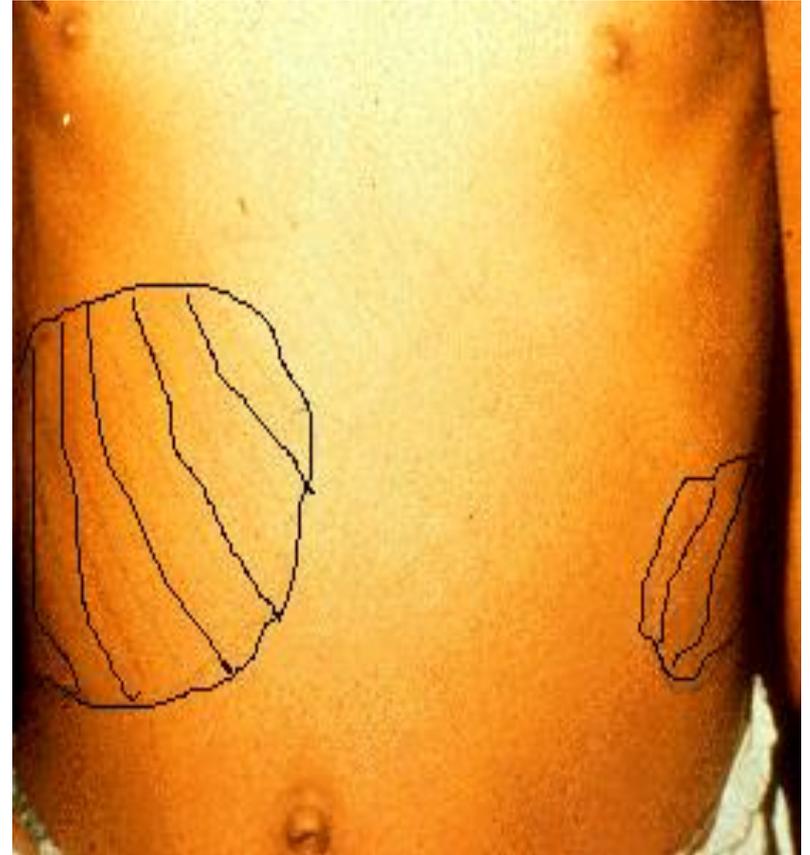


Exudative pharyngotonsillitis

Infectious Mononucleosis



Cervical
lymphadenopathy



Hepatosplenomegaly

Infectious Mononucleosis



IM with rash after treatment with amoxicillin or ampicillin

Infectious Mononucleosis

- **Acute infectious mononucleosis**
 - fatigue and malaise 1-2 wks
 - sore throat, pharyngitis
 - retro-orbital headache
 - fever
 - myalgia
 - nausea
 - abdominal pain
 - generalized lymphadenopathy
 - Hepatosplenomegaly



Burkitt's Lymphoma

- Burkitt's lymphoma (BL) occurs endemically in parts of Africa (where it is the commonest childhood tumor) and Papua New Guinea. It usually occurs in children aged 3-14 years. It responds favorably to chemotherapy.
- It is restricted to areas with holoendemic malaria. Therefore it appears that malaria infection is a cofactor.
- Multiple copies of EBV genome and some EBV antigens can be found in BL cells and patients with BL have high titres of antibodies against various EBV antigens.

Burkitt Lymphoma

EBV+: 90% of cases in developing countries – jaw tumors

20% cases in US – children with abdominal tumors

AIDS patients – tumors in lymph nodes

Therapy: Chemotherapy



Burkitt's Lymphoma

- BL cells show a reciprocal translocation between the long arm of chromosome 8 and chromosomes 14, 2 or 22.
- This translocation result in the c-myc oncogene being transferred to the Immunoglobulin gene regions. This results in the deregulation of the c-myc gene. It is thought that this translocation is probably already present by the time of EBV infection and is not caused by EBV.
- Sporadic cases of BL occur, especially in AIDS patients which may or may not be associated with EBV.
- In theory BL can be controlled by the eradication of malaria (as has happened in Papua New Guinea) or vaccination against EBV.

B-Cell Lymphoma

- 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.

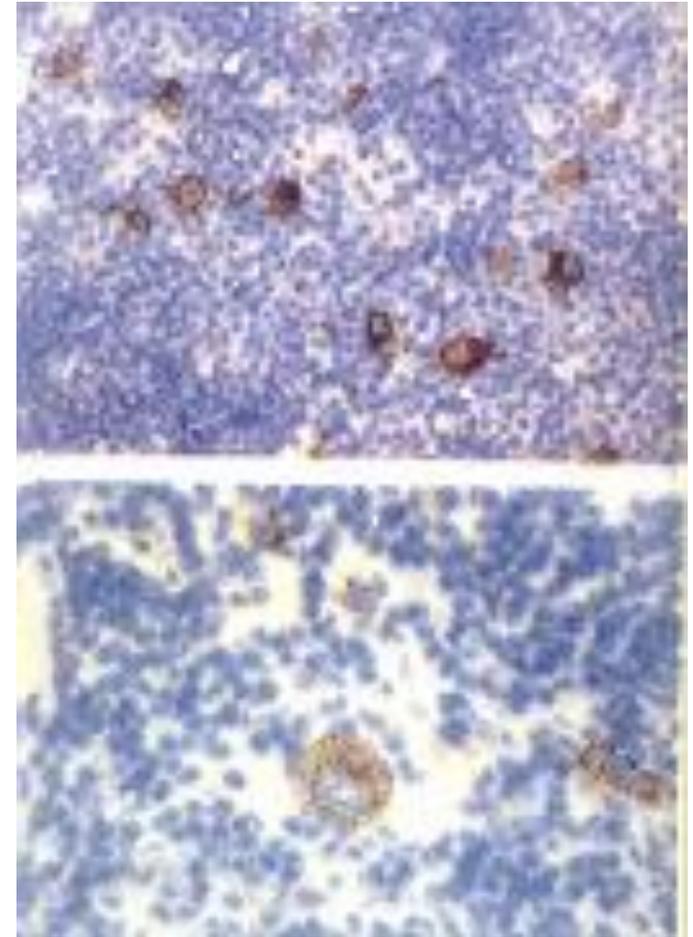
Hodgkin Disease

EBV+: 60-70% of cases in developing countries

35-50% cases in US

EBV in Reed-Sternberg cells

Therapy: Chemotherapy, radiation
Anti-EBV CTLs effective in some cases



LMP-1 expression

Nasopharyngeal Carcinoma

- Nasopharyngeal carcinoma (NPC) is 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.
- The tumor is rare in most parts of the world, though pockets occur in N. and C. Africa, Malaysia, Alaska, and Iceland.
- 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.
- In theory NPC can be prevented by vaccination.

Immunocompromised Patients

- After primary infection, EBV maintains a steady low grade latent infection in the body. Should the person become immunocompromised, the virus will reactivate. In a few cases, lymphoproliferative lesions and lymphoma may develop. These lesions tend to be extranodal and in unusual sites such as the GI tract or the CNS.
- **Transplant recipients** e.g. renal - EBV is associated with the development of lymphoproliferative disease and lymphoma.
- **AIDS patients** - EBV is associated with oral leukoplakia and with various Non-Hodgkin's lymphoma.
- **Duncan X-linked lymphoproliferative syndrome** - this condition occurs exclusively in males who had inherited a defective gene in the X-chromosome . This condition accounts for half of the fatal cases of IM.

Molecular Biology : Replication

- Viral capsid antigens (VCAs) are the primary structure proteins in viral capsids and are found in replicating cells.
- EBV early antigens (EAs) consist of >15 proteins codes by genes distributed throughout the genome.
- EBV nuclear antigen (EBNA) corresponds to six virally encoded proteins found in the nucleus of an EBV-infected cell.

Molecular Biology : Latency

- Latently infected B cells are the primary reservoir of EBV in the body.
- >100 gene products may be expressed during active viral replication, only 11 are expressed during viral latency.
- In this way, the virus limits cytotoxic T-cell recognition of EBV-infected cells.

Diagnosis

- Acute EBV infection is usually made by the heterophil antibody test and/or detection of anti-EBV VCA IgM.
- Cases of Burkitt's lymphoma should be diagnosed by histology. The tumour can be stained with antibodies to lambda light chains which should reveal a monoclonal tumour of B-cell origin. In over 90% of cases, the cells express IgM at the cell surface.
- 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.**
- A patient with with non-specific ENT symptoms who have elevated titers of EBV IgA should be given a thorough examination.

Infectious Mononucleosis : Lab

- The white blood cell 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.
- Atypical lymphocytes are enlarged lymphocytes that have abundant cytoplasm, vacuoles, and indentations of the cell membrane.
- CD8 cells predominate among the atypical lymphocytes.
- Low-grade neutropenia and thrombocytopenia are common during the first month of illness.
- Liver function is abnormal in more than 90% of cases.
- Serum levels of aminotransferases and alkaline phosphatase are usually mildly elevated.

Infectious Mononucleosis : Lab

- Heterophile antibody titers rise during the first two or three weeks with half or more developing a significant titer during the first week of illness. (50% in first week of illness)
- 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.
- Heterophile antibody most commonly used in the serological diagnosis of IM is an IgM antibody which agglutinates sheep red blood cells.

Infectious Mononucleosis : Lab

–Time course of antibody production

- EA is rising at symptom onset : rise for 3-4 weeks, then quickly decline to undetectable levels by 3-4 months, although low levels may be detected intermittently for years.
- VCA-IgM usually is measurable at symptom onset, peaks at 2-3 weeks, then declines and unmeasurable by 3-4 months.
- VCA-IgG rises shortly after symptom onset, peaks at 2-3 months, then drops slightly but persists for life.
- **EBNA** : convalescence and remain present for life.

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	+	-	+/-	+

IM treatment

- Therapy for IM consists of 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.
- If splenic rupture occurs, splenectomy is required.
- Acyclovir, at a dosage of 400 to 800 mg five times daily, has been effective for the treatment of oral hairy leukoplakia (despite common relapses) and some cases of chronic active EBV disease.
- The posttransplantation EBV lymphoproliferative syndrome generally does not respond to antiviral therapy.
- When possible, therapy should be directed toward reduction of immunosuppression .

IM treatment

- **Interferon .**
- antibody to CD20.
- Infusions of donor lymphocytes are often effective for stem cell transplant recipients.
- Infusions of EBVspecific cytotoxic T cells.
- Infusion of autologous EBV-specific cytotoxic T lymphocytes
- The isolation of patients with IM is unnecessary.

Summary

- In addition to clinical signs and symptoms, laboratory testing is necessary to establish or confirm the diagnosis of IM. This can provide important information for both the diagnosis and management of EBV-associated disease.
- If the classic signs and symptoms of IM are absent, a diagnosis of IM is more difficult to make. A definite diagnosis of IM can be established by serologic antibody testing. The antibodies present in IM are heterophile and EBV antibodies.
- EBV is widely disseminated. It is estimated that 95% of world's population is exposed to the virus, which makes it the most ubiquitous virus known to man.
- EBV is only a minor problem for immunocompetent persons, but it can become a major one for immunologically compromised patients
- After primary exposure a person is considered to be immune and generally no longer susceptible to overt reinfection.