Epstein-Barr Virus (EBV or HHV4)

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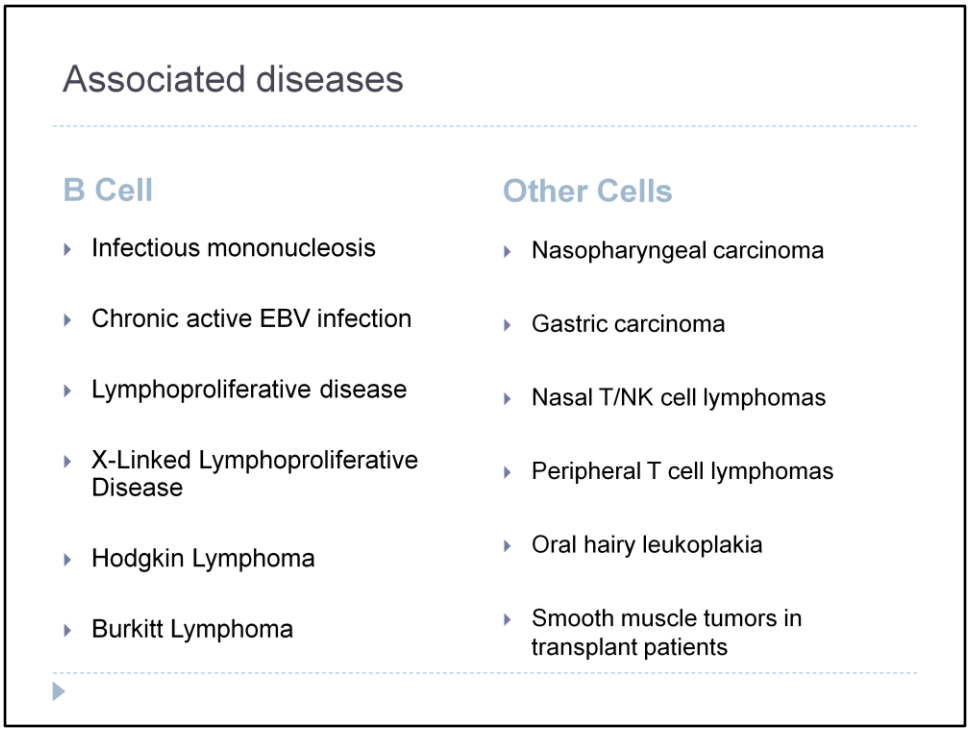
Key facts

- Widely disseminated herpesvirus
  - ~90-95% of adults are EBV-seropositive
- Spread by contact with infected saliva
- Primary EBV infections worldwide are mostly subclinical
  - Developing countries: early infection 3-6yrs/subclinical
  - Developed countries: later 10-30yrs/clinically apparent
- EBV has a latency phase (~10% of viral proteins are expressed)
- Host cells:
  - B/T lymphocytes
  - Epithelial cells
  - Myocytes

Rarely also through, blood, transplants, unprotected sex, and intrauterine without adverse affects to the fetus

Subtypes

- 2 subtypes:
  - EBV1 (type A): Developed countries
  - EBV2 (type B): Equatorial Africa, New Guinea
- Co-infection has been reported in immunocompromised patients, particularly those with HIV infections

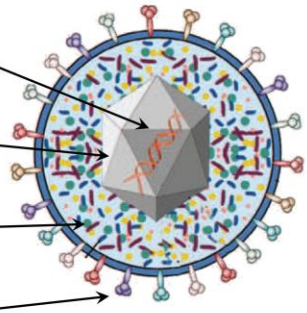


EBV can cause transformation

Molecular Biology

Structure

- Toroid-shaped protein core wrapped with linear double-stranded DNA
- Icosahedral nucleocapsid
- Amorphous protein tegument surrounding the capsid
- Outer envelope containing glycoprotein spikes

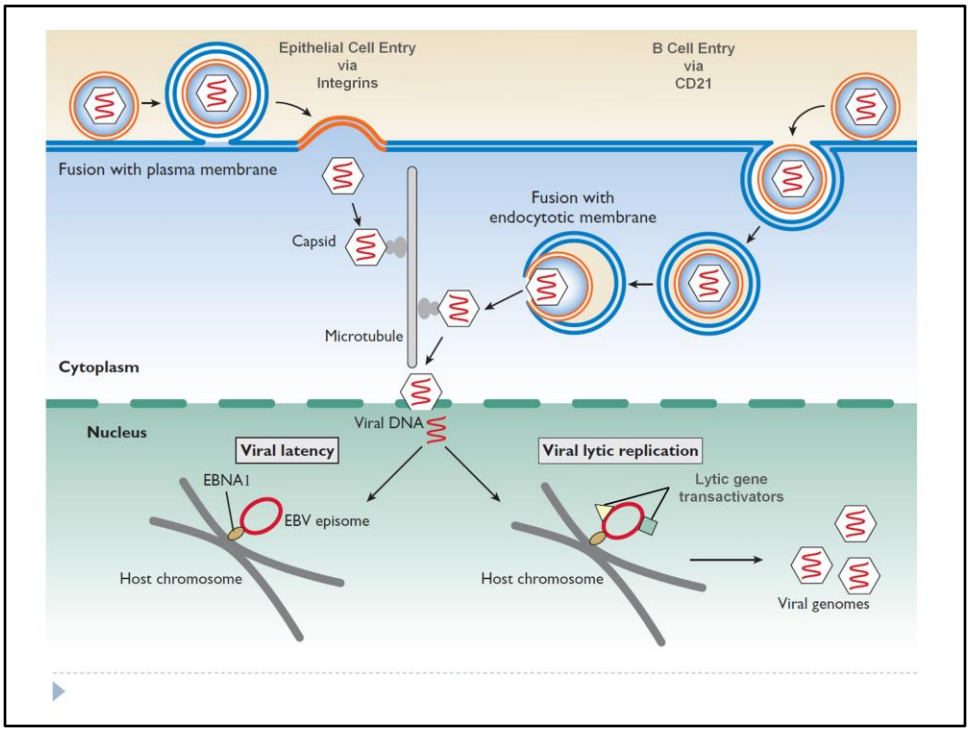


Toroid means donut shaped

Icosahedral means twenty faces

Tegument contains proteins/enzymes important for replication

Envelope is lipid membrane acquired when budding out of the cell, it has the glycoprotein spikes required for attachment/infection gp350/220.



B cells and epithelial cells are the major sites for EBV infections in humans

CD21 is a complement receptor

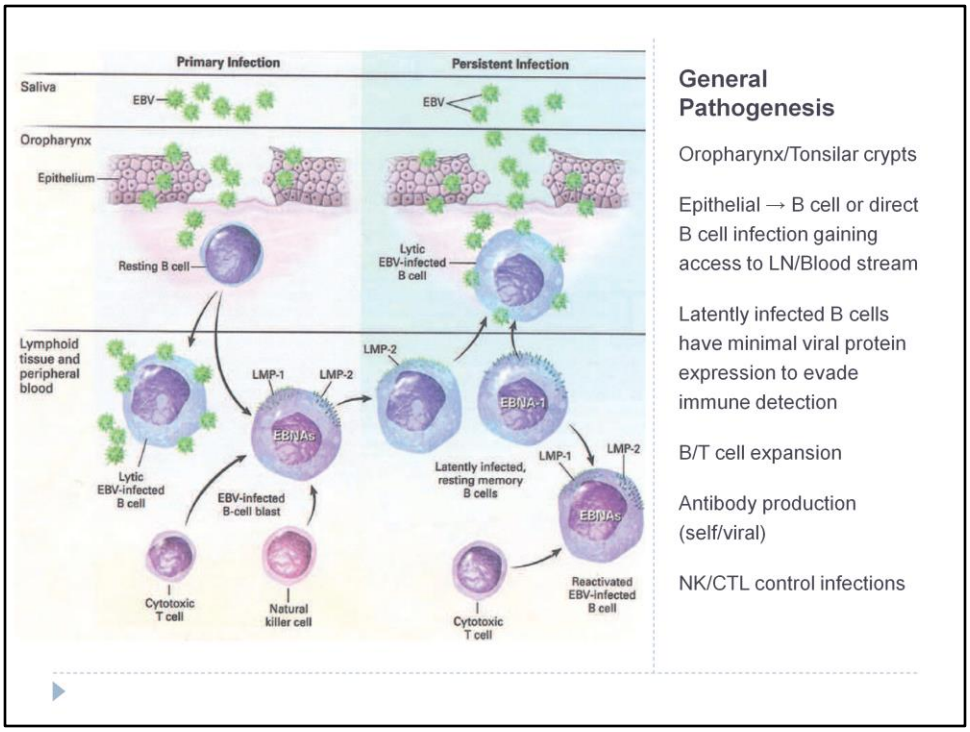
Linear EBV genome becomes circular, forming an episome

Viral latency not to be confused with clinical latency where the virus is active.

Latent B cells may be transformed (immortalized) to replicate indefinitely. Cancer link. No difference in cancer induction between subtypes.

Epithelial infection is lytic

EBNA = EBV nuclear antigen



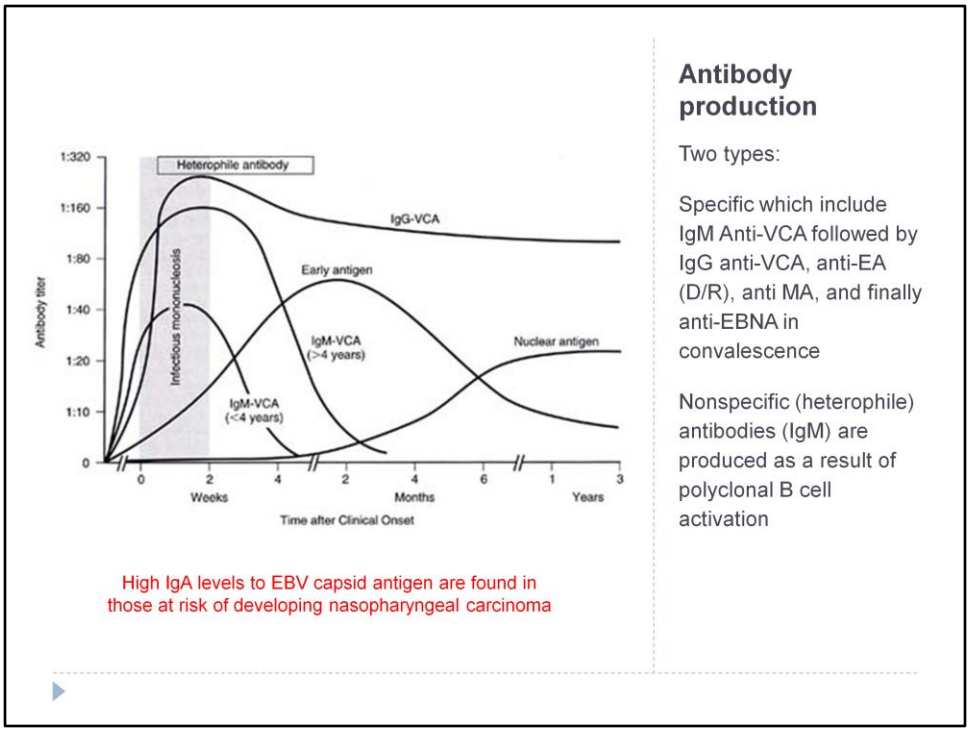
lymphocytes in the tonsillar crypts can be infected directly

NK/CTL (cellular immunity) are more important in controlling EBV infection than antibodies (humoral immunity)

Initial control of EBV infection is due to NK cells and non–HLA-specific cytotoxic T cells, while later during convalescence HLA-specific CD8 and CD4 T cells are important for control of infection. T cell response is responsible for reducing EBV infected B cells.

Antibody is likely important for protection against IM but may not be sufficient to prevent infection; vaccine trials using gp350 as an immunogen showed reduction of IM but no difference in infection

When patients are treated with acyclovir, shedding of EBV from the oropharynx stops but the virus persists in B cells.



Early antigen EA-D (diffuse, nucleus/cytoplasm) in IM, nasopharyngeal carcinoma (NPC) or chronic active EBV (CAEBV)

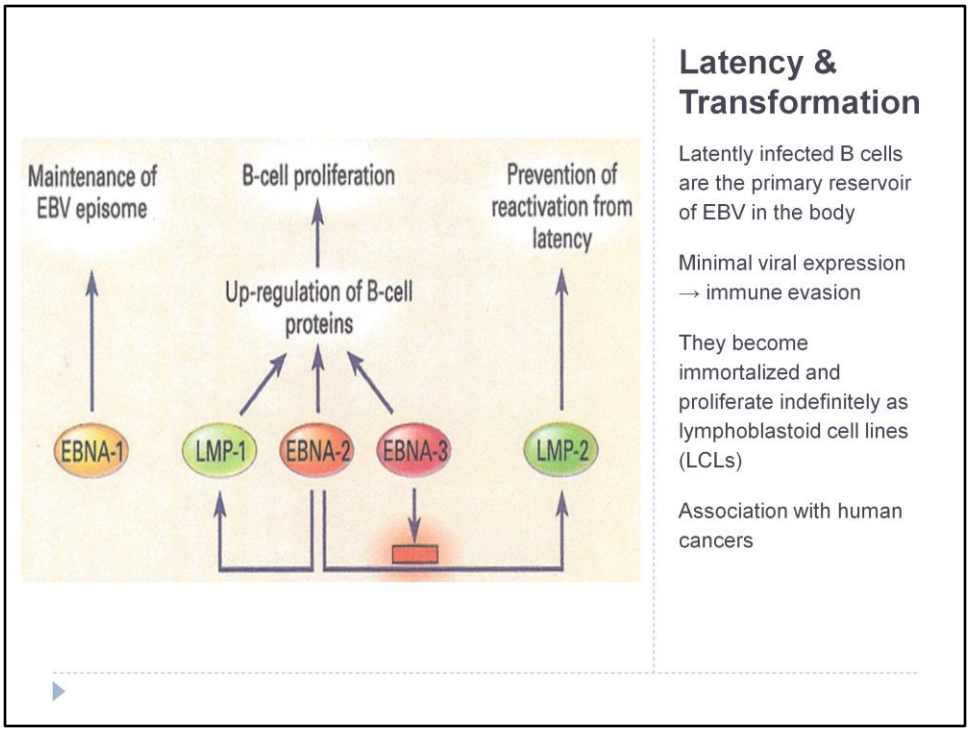
EA-R (restricted, cytoplasm) in BL & CAEBV

MA = membrane antigen (gp350/220) that binds to CD21

Heterophile antibodies persist for up to 1 year after IM and are often absent in children younger than 5 years old or in the elderly. They are non-EBV specific antibodies resulting from polyclonal B cell expansion. They have broad reactivity with antibodies of other animal species.

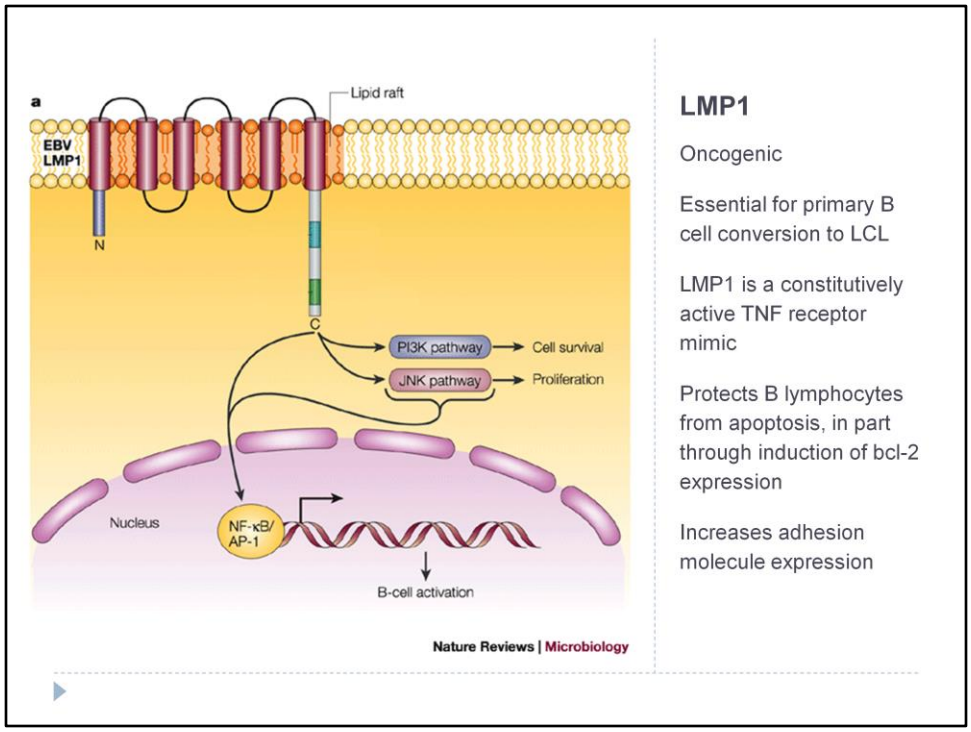
EBV Serology

Condition	Result in Indicated Test					
		Anti-VCA		Anti-EA		
	Heterophile	IgM	IgG	EA-D	EA-R	Anti-EBNA
Acute infectious mononucleosis	+	+	++	+	–	–
Convalescence	±	–	+	–	±	+
Past infection	–	–	+	–	–	+
Reactivation with immunodeficiency	–	–	++	+	+	±
Burkitt's lymphoma	–	–	+++	±	++	+
Nasopharyngeal carcinoma	–	–	+++	++	±	+

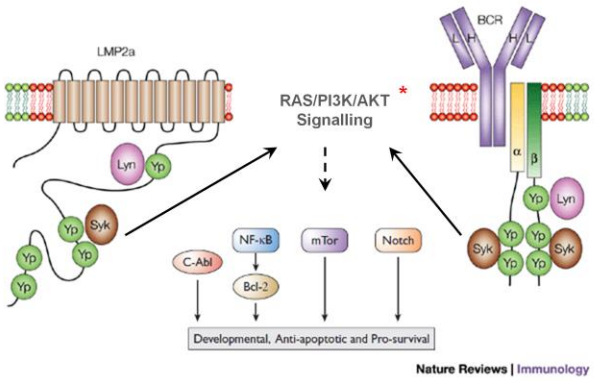


Memory B cells are the reservoir

Latent infection can persist throughout one's lifetime



Adhesion molecule increase = cell clumping typical of primary infections



LMP2

LMP2 constitutively mimics signalling from the B-cell receptor

Upregulates CD21

EBV latent membrane proteins mimic two signals that are essential for normal B-cell development and function

* Others not shown

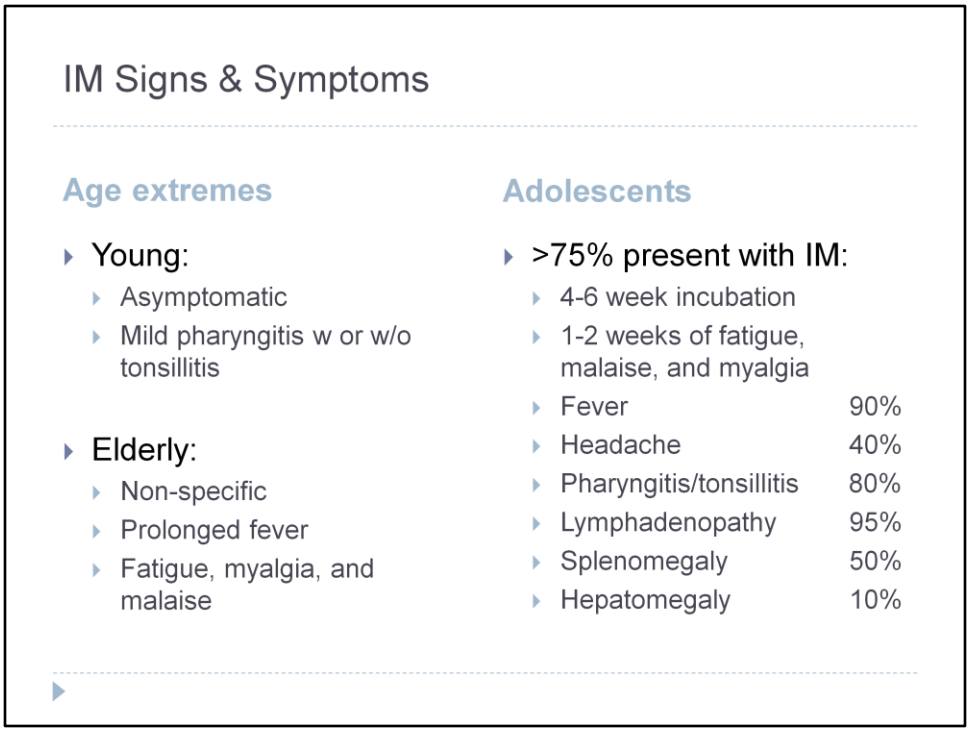
Clinical Syndromes

Infectious mononucleosis

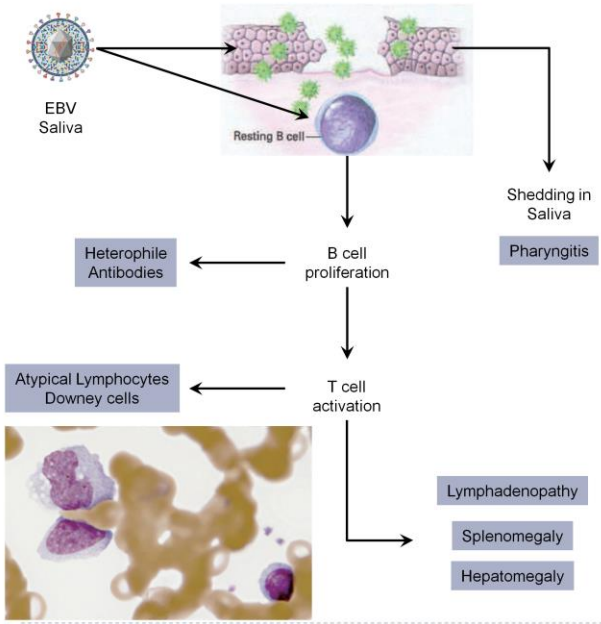
(mono, Drüsenfieber, glandular fever, Pfeiffer's disease, Filatov's disease, and the kissing disease)

- Nil Filatov 1885, Emil Pfeiffer 1889
  - fever
  - lymphadenopathy
  - malaise
  - hepatosplenomegaly
  - abdominal discomfort in adolescents and young adults
- 1920, Sprunt & Evans coined the term IM
- 1923, Downey and McKinlay detailed description of the lymphocyte morphology
- 1932, Paul & Bunnell identified heterophile antibodies in serum during acute IM
- 1968, Henle reported the relationship between acute IM and EBV

Plenty of reported cases in the early 1900's that were consistent with IM



Eyelid edema may be present in the first week 15%



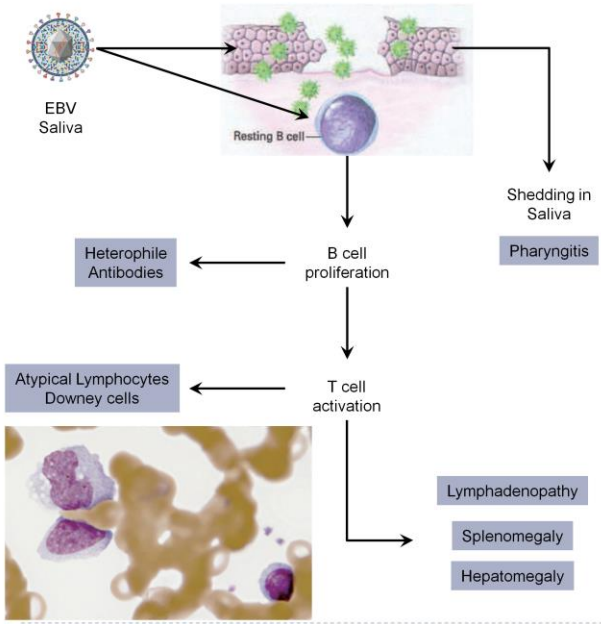
IM Pathogenesis

First 2 weeks:

Symmetrical non-fixed mildly tender LA, commonly posterior cervical LN, epitrochlear LN involvement very suggestive of IM

Pharyngitis is the most consistent physical finding,1/3 exudative

Tonsillar enlargement may obstruct airway



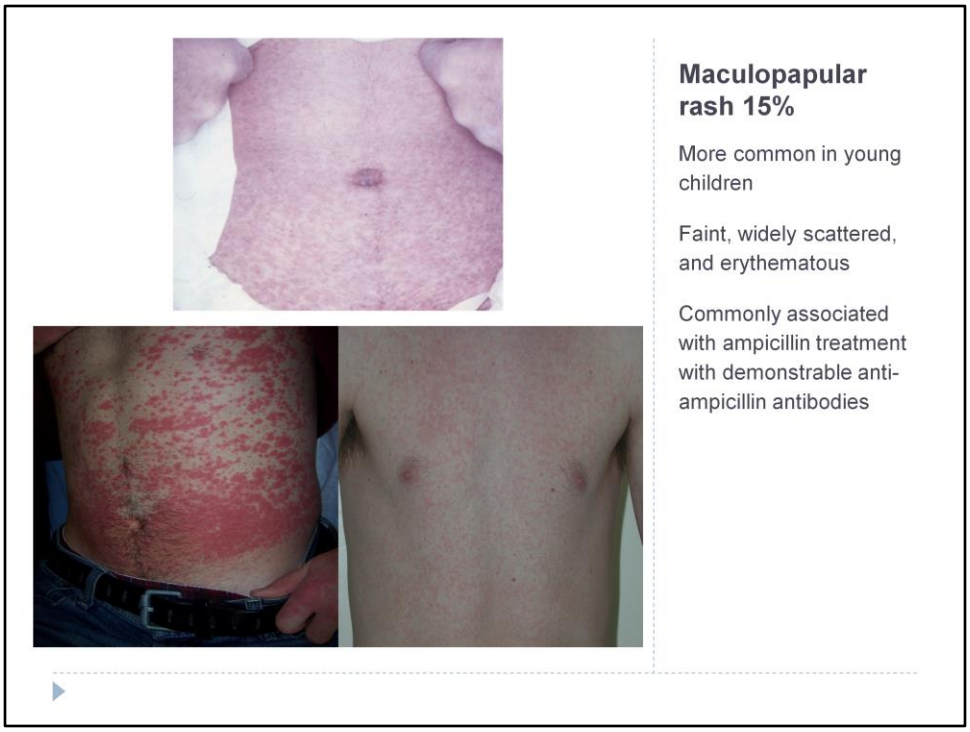
IM Pathogenesis

Weeks 2-3:

Palpable splenomegaly, at risk of spontaneous rupture or due to mild trauma.

Tender hepatomegaly, jaundice is rare

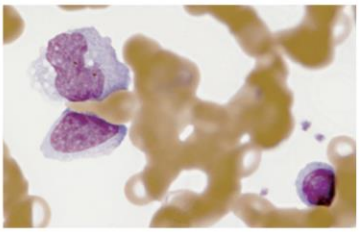
More common in younger children with IM



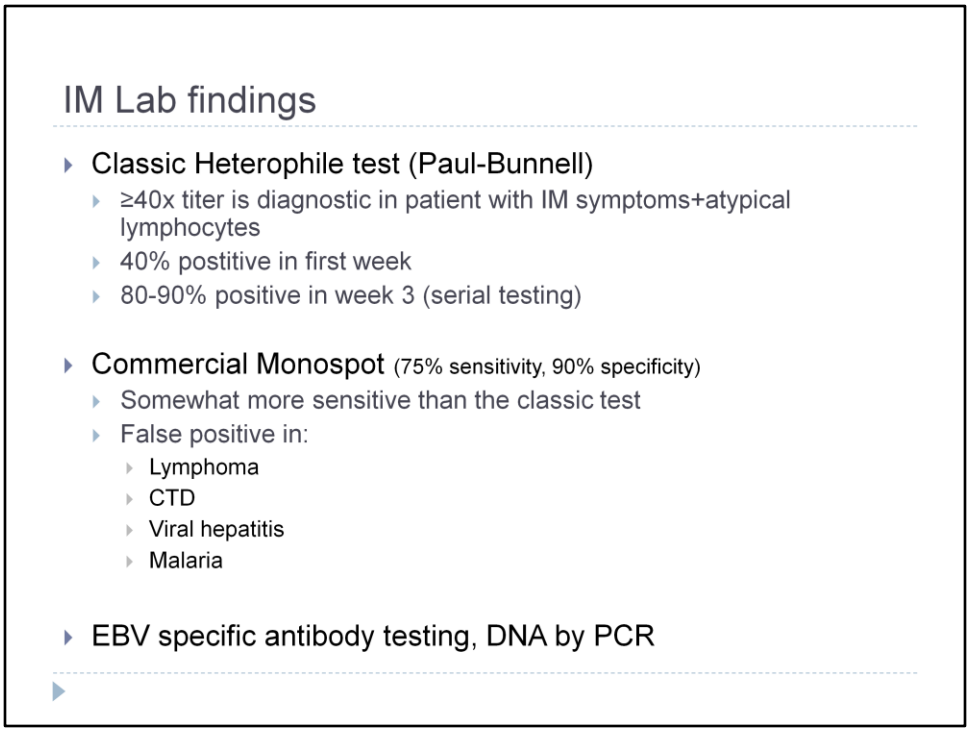
Young children also have symptoms of upper respiratory tract infection

IM Lab findings

- Elevated WBC count (weeks 2-3)
- Lymphocytosis with >10% atypical lymphocytes
  - Enlarged with abundant cytoplasm, vacuoles, & indentations of the cell membrane
  - Mostly CD8+



- Low-grade neutropenia and thrombocytopenia (first month)
- Liver function is abnormal in >90% of cases



heterophile titer is defined as the greatest serum dilution that agglutinates sheep, horse, or cow erythrocytes

CTD = connective tissue disease

EBV-specific antibody testing is used for patients with suspected acute EBV infection who lack heterophile antibodies and for
patients with atypical infections

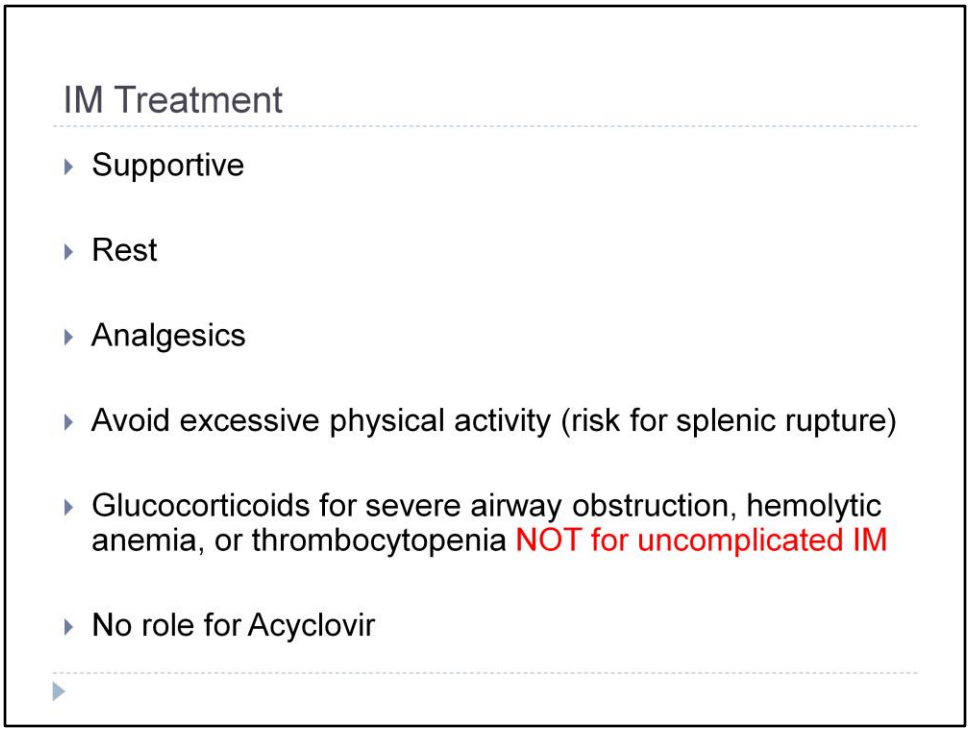
IgM antibody to VCA is most useful for the diagnosis of acute IM because it is present at elevated titers only during the first 2–3 months of the disease; in contrast, IgG antibody to VCA is usually not useful for diagnosis of IM but is often used to assess past exposure to EBV because it persists for life.

The polymerase chain reaction has been used to detect EBV DNA in the CSF of some AIDS patients with lymphomas and to monitor the amount of EBV DNA in the blood of patients with lymphoproliferative disease. Detection of high levels of EBV DNA in blood during the first few weeks of IM may be useful if serologic studies yield equivocal results.

IM Complications

- Most cases are self-limiting
- Death is rare, most commonly due to:
  - CNS complications (Meningitis, Encephalitis, Guillain Barré syndrome)
  - Splenic rupture
  - Upper airway obstruction
  - Bacterial superinfection
- Other complications:
  - Hepatitis
  - Hemolytic anemia
  - Thrombocytopenia
  - Autoimmune disease

Guillain Barré polyneuropathy affecting peripheral and autonomous due to self reacting antibodies. Life threatening if affecting respiratory muscles.



Glucocorticoids can predispose for bacterial superinfection

Whereas ~90% of cases of IM are due to EBV, 5–10% of cases are due to cytomegalovirus (CMV). CMV is the most common cause of heterophile-negative mononucleosis

Chronic Active EBV

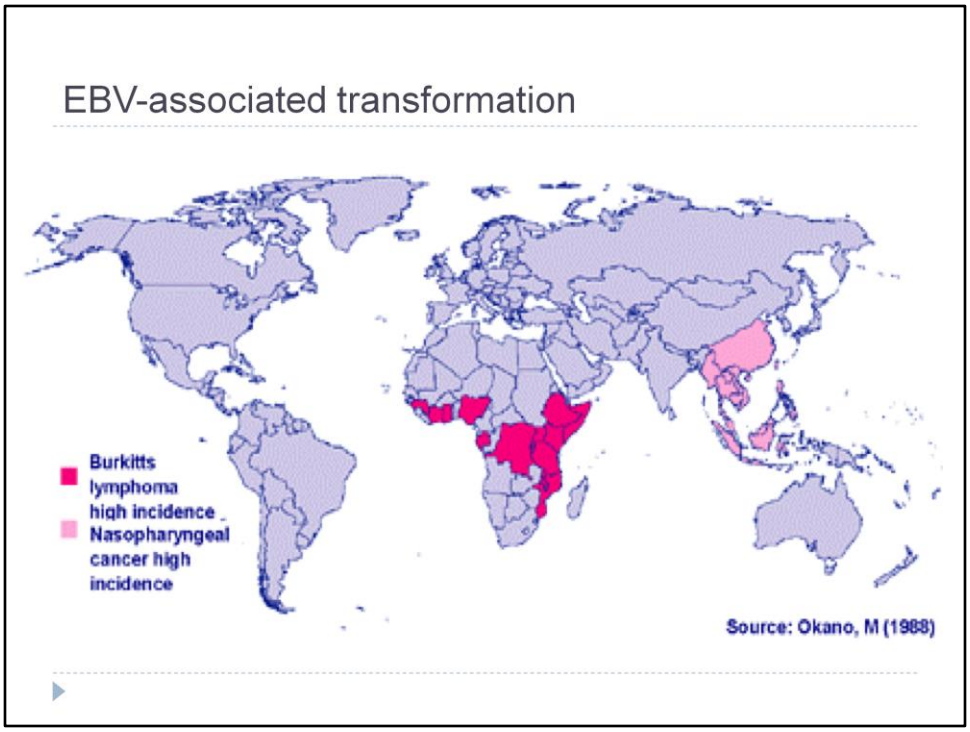
- Rare
- Not a cause of chronic fatigue syndrome, but presents like it
- Illness lasting >6 months
- Elevated levels of EBV DNA in the blood
- Very high titers of anti-EBV antibodies
- Evidence of organ involvement:
  - Hepatosplenomegaly
  - Lymphadenopathy
  - Pneumonitis
  - Uveitis
  - Neurological involvement

Patients often have low levels of EBV-specific CD8 T cells, implying a failure to control infection

EBV-associated transformation

- 1920, Sprunt and Evans published cases of spontaneously resolving acute leukemia associated with blast-like cells in the blood
- 1958, Dennis Burkitt described cases of “round-cell sarcoma” (Lymphoma) in children & adolescents in Uganda
- 1964, Epstein described the first human tumor virus in a Burkitt lymphoma cell line by EM

PTLD = post transplant lymphoproliferative disease



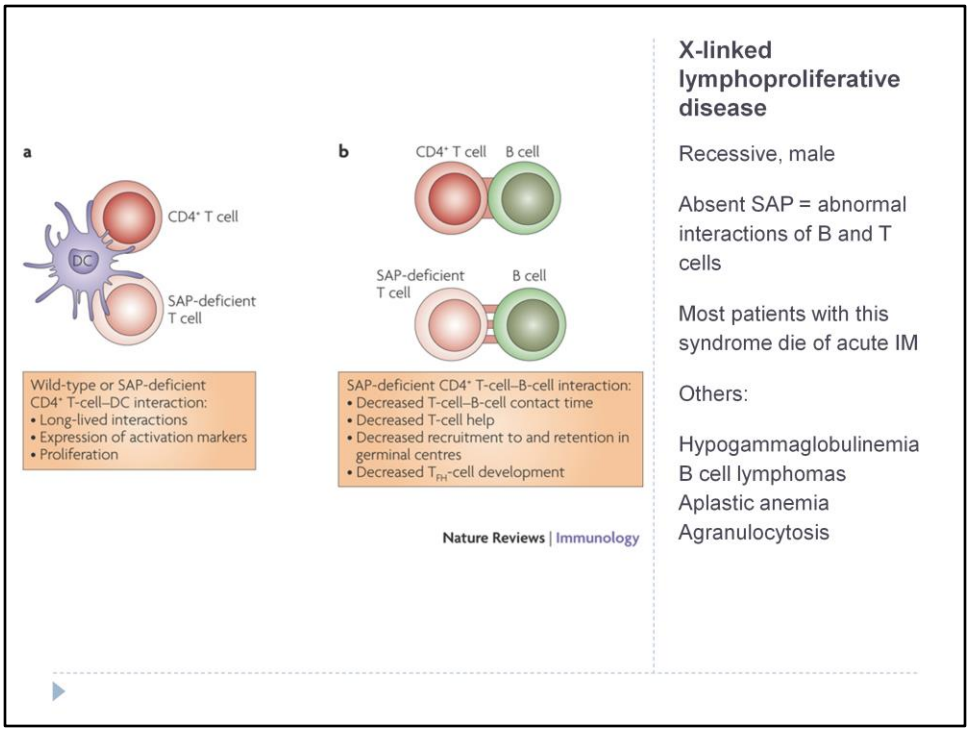
BL in africa may be related to endemic malaria impairing cellular immunity and increasing B cell expansion

NPC association with south east asia is less clear. Potential dietary habits, Chinese migrants to the US still have higher incidence of NPC, rates in southeast asia are going down = change in dietary habits?

EBV-associated lymphoproliferative disease

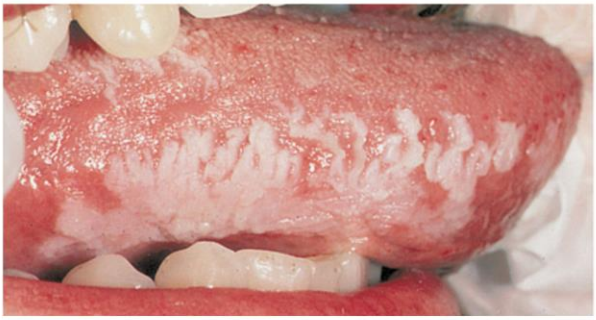
- Occurs in patients with congenital or acquired immunodeficiency:
  - SCID
  - AIDS
  - Transplant patients receiving immunosuppressive drugs (PTLD)
  - RA patients on methotrexate
- Impaired T-cell function = inability to control EBV-infected B cells
- Proliferating EBV-infected B cells infiltrate LN & organs
- Pathology ranges from polymorphic lymphoproliferative disease to diffuse large B-cell lymphoma

PTLD = post transplant lymphoproliferative disease. Reduction in immune suppression may allow T cells to develop, surgery for focal lesions…



Recessive disorder of young boys who have a normal response to childhood infections but develop fatal lymphoproliferative disorders after infection with EBV

Other mutations have also been reported with SAP deficiency being the most common



Oral Hairy Leukoplakia

Early manifestation of infection with HIV in adults

Caused by EBV

Non-malignant, non-removable, non-painful, epithelial hyperplasia

No treatment required

Highly responsive to Acyclovir but recurs

EBV induced proliferation disorders are more common in an immunocompromised state, there are some non-imunocompromised tumors that are also EBV related. They are less common and outside of the scope of this lecture.