



HLS SYSTEM

Sub: Microbiology

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Lec no: 1

Title: Epstein barr virus and parvovirus B19



Epstein Barr Virus

EBV

By

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طبعاً بما انه عرفنا نظام دكتوراة هالة بالاسئلة فرح اعتمد بتفريغي على
اني اكتب الشغلات يلي حكت عنها مهمة ، او الاسئلة المتوقعة ، و اذا
في اشى مش مفهوم رح اوضحه ان شاء الله ..



Introduction

- Epstein-Barr virus (EBV) named after discoverers Epstein & Barr in 1964.
- It is a member of **herpesvirus family** with special tropism to B lymphocyte.
- It is the causative agent of **acute infectious mononucleosis** and is associated with several cancers, namely **Burkitt's lymphoma**, some forms of **Hodgkin's lymphoma**, and **nasopharyngeal carcinoma**.

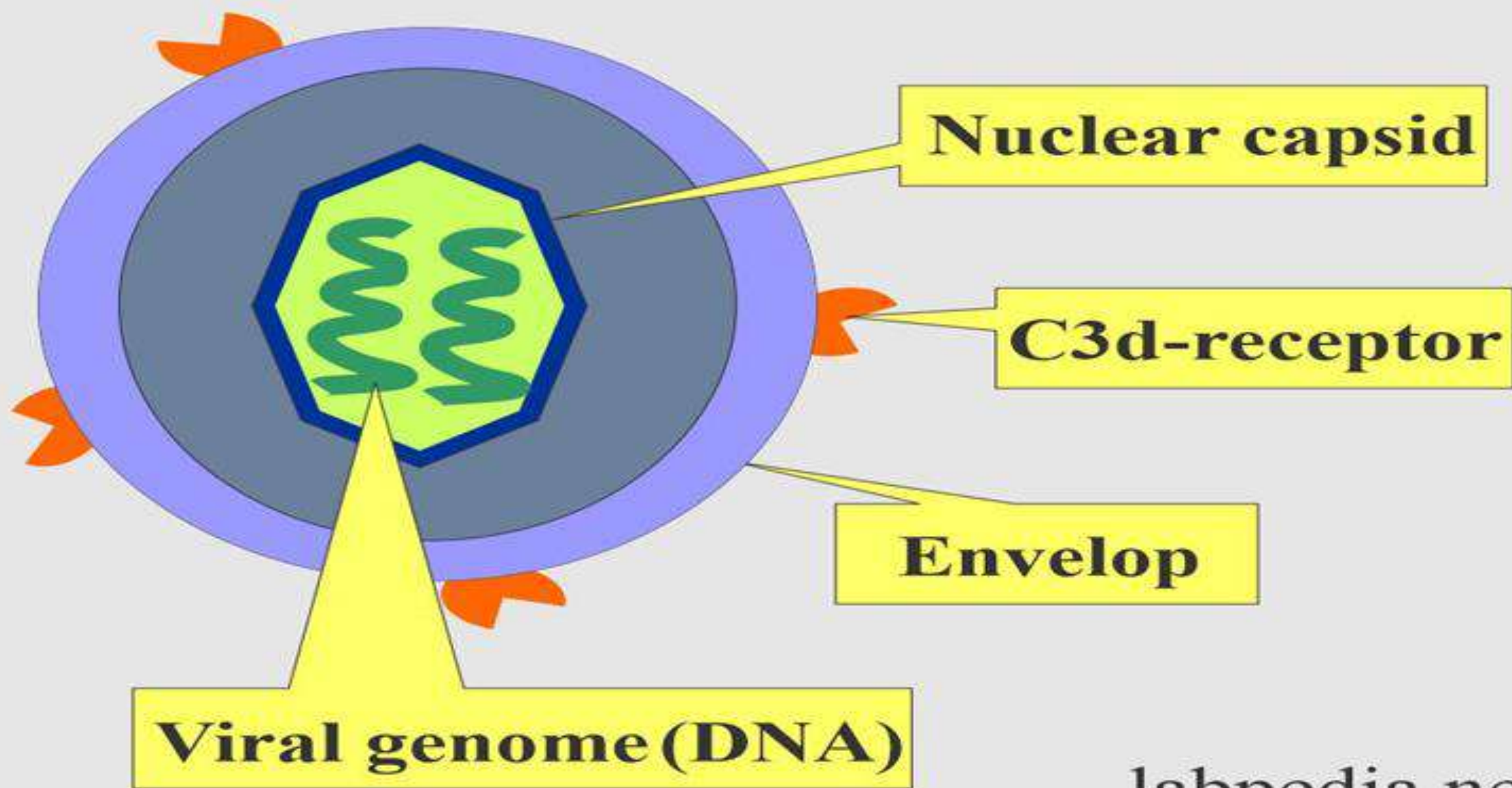
كله اخذناه الفصل الماضي

It is structurally and morphologically similar to other herpesviruses:

- **Virion:** Spherical, 150–200 nm in diameter.
- **Enveloped.**
- **Capsid:** icosahedral symmetry.
- **Genome:** Double-stranded DNA.
- **Replication:** In the nucleus.
- They produce large, acidophilic, intranuclear inclusion bodies.
- The ability to establish latent infection with periodic reactivation.

كله اخذناه الفصل الماضي

Epstein-Barr-Virus



هي عبارة عن بروتينات على سطح الفيروس ، مهم اعرفها طبعا لانه بتكون لها antibodies ، و هذا
الاشي مهم في ال diagnosis of disease

Viral antigens:

- **Viral capsid antigen (VCA):** The most important antigen because it is used most often in diagnostic tests.
- **Early antigens (EA):** which are produced prior to viral DNA synthesis.
- **Epstein–Barr nuclear antigen (EBNA):** located in the nucleus and needed to maintain the viral DNA episomes in the infected cells and (immortalization of B lymphocytes (latent infection)).
هو يلي بحافظلي على ظاهرة ال latency ، حيث انه هذا الفيروس ما يغادر الجسم و بضل موجود بال dorsal ganglia على شكل episomes
- **Viral membrane antigen:** Neutralizing antibodies that prevent re-infection are directed against the viral membrane antigen.
مصدره من ال envelop

هذا ال antigen بخلي الخلية تدخل بحالة اسمها ال immortalization ، يعني بخلي الخلية تنقسم بشكل غير متناهي بدون ما تموت

ال antibody المسؤولة عن منع ال reinfection بترتبط بهذا ال antigen (life long immunity)

The immune response to EBV infection:

A) Cell mediated immunity **Cytotoxic T lymphocytes** react against the infected B cells.

B) Humoral immunity:

1- Early in acute disease: transient rise of **VCA-IgM**, which is rapidly followed by **VCA-IgG**, which persist for life

2- Slightly later: Antibodies to **EA** develop and persist for several weeks.

3- Several weeks after acute infection : Antibodies to **EBNA** arise and persist for life.

4- **Lifelong immunity** against infection is based on antibody to **viral membrane antigen**.

N.B. In addition to the EBV-specific antibodies, **non-specific heterophil antibodies** are formed and can agglutinate sheep or horse red blood cells in the laboratory. Heterophil antibodies usually disappear within 6 months after recovery.



VCA IgM

VCA IgG

EAD IgG

EBNA IgG

Incubate

Acute

Convalescent

شو بستفيد من هاي الصورة :

بقدر اعرف اذا المريض في حالة ال acute infection (مصاب حديثا) ، او في حالة ال coalescent infection (كان مصاب) ، و هذا عن طريق ال antibodies يلي بشوفها في ال serum

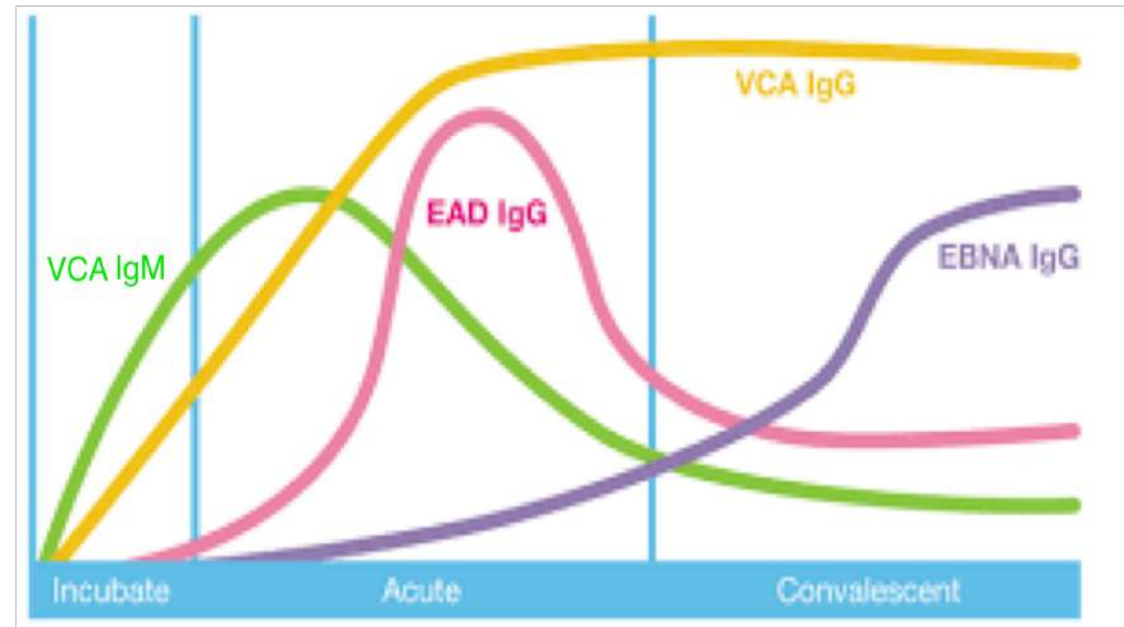
اذا كان في :

(VCA IgM مع VCA IgG)
أو
(VCA IgM) فقط

بكون : acute infection

اما اذا لقيت :
EBNA IgG أو VCA IgG

بكون : convalescent infection



VCA-IgM	VCA-IgG	EA-D, IgG	EBNA, IgG	Interpretation
Negative	Negative	Negative	Negative	No Infection
Positive	Positive	Negative	Negative	Early Infection
Negative / Positive	Positive	Positive	Negative	Active Infection
Negative	Positive	Negative	Positive	Past Infection
Negative	Positive	Positive	Positive	Indicate Reactivation of Virus

VCA-IgM	VCA-IgG	EA-D, IgG	EBNA, IgG	Interpretation
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Negative / Positive	Positive	Positive	Negative	Active Infection
Negative	Positive	Negative	Positive	Past Infection
Negative	Positive	Positive	Positive	Indicate Reactivation of Virus

Diseases caused by EBV:

انتبه انه احنا حكينا انه هذا الفايروس هو مرتبط ببعض انواع الكانسر ، يعني مش ضروري يسبب
كانسر ، طيب كيف يعني مرتبط ؟
حكينا سابقا انه هذا الفايروس يدخل الخلية بحالة ال immortalization ، وبخليها تنقسم بشكل غير
متناهي

A) Primary infection producing **infectious mononucleosis (I.M) (glandular fever)**.

B) EBV infection is associated with development of several tumors (especially in AIDS patients):

➤ **Burkitt's lymphoma**, (a tumor of the jaw). →

➤ **Some forms of Hodgkin's lymphoma**.

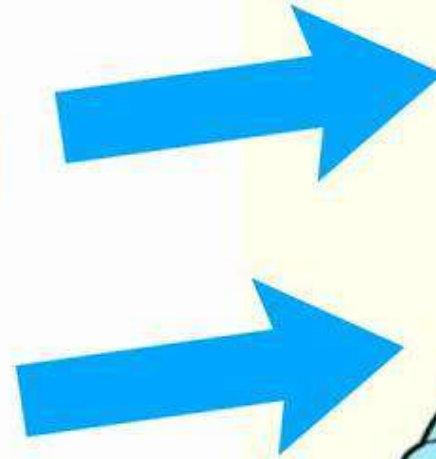
➤ **Nasopharyngeal carcinoma**.

➤ **Hairy leukoplakia**, a whitish, nonmalignant lesion with an irregular "hairy" surface on the lateral side of the tongue.



MONONUCLEOSIS

"KISSING DISEASE"



Pathogenesis:

Primary Infection

- EBV is transmitted by infected **saliva** (so called kissing disease).
- Infection starts in the **oropharynx**, resulting in **the prominent sore throat**.
- Then spreads to the blood, where it **infects B lymphocytes** (The major target cell for EBV) through binding to the viral receptor (**CD21**, receptor of C3 complement) on B cell where it become **transformed and proliferated**.
- In normal individuals, most virus-infected cells are eliminated, but small numbers of latently infected lymphocytes persist for the lifetime of the host (one in 10^5 – 10^6 B cells).

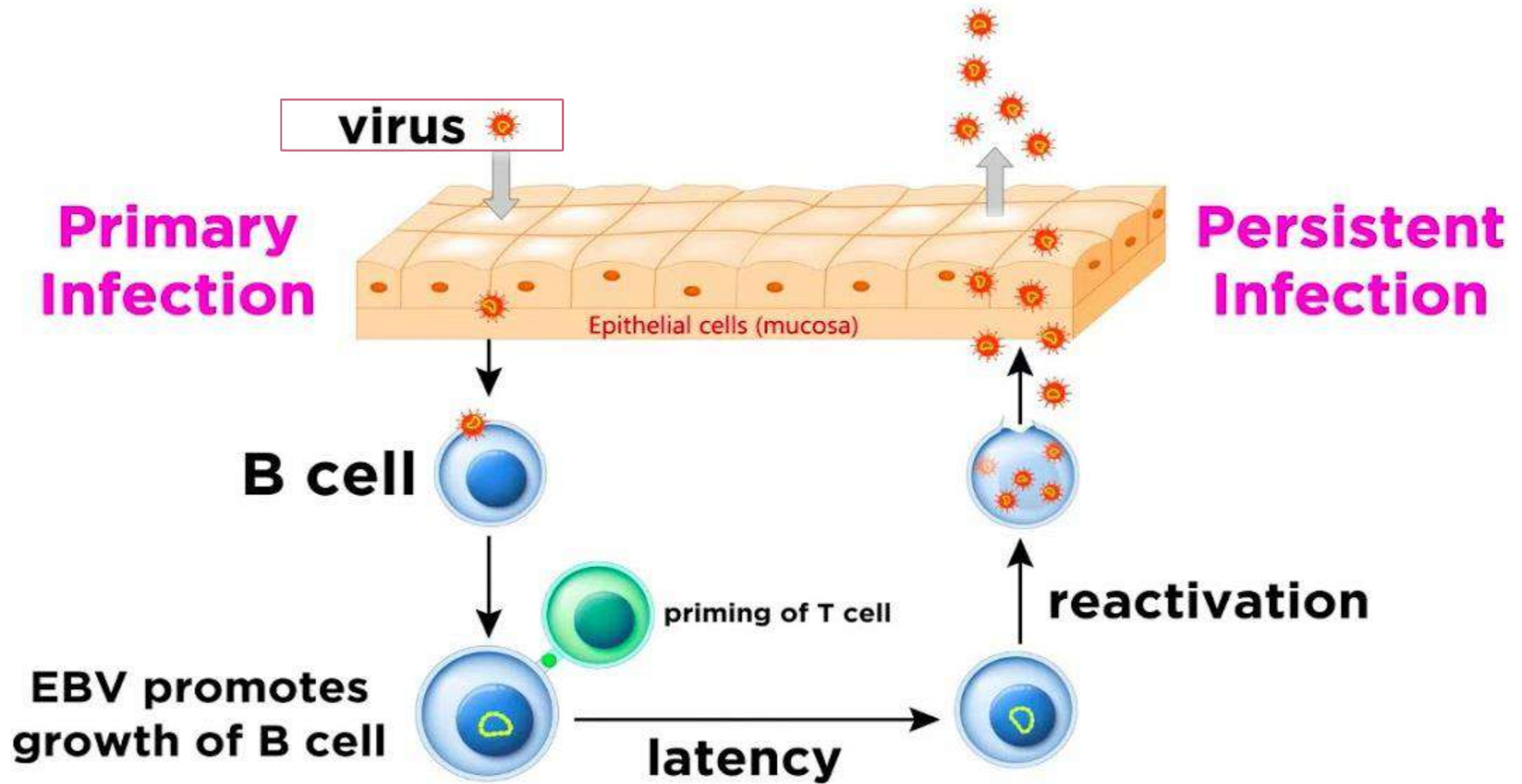
N.B. The viral DNA remains **latent in the nucleus of B lymphocytes**, but **NOT integrated into cellular DNA**).

Reactivation from Latency

- Reactivations of EBV latent infections can occur, as result of **Immunosuppression**.
- **These are usually clinically silent**, however, sometimes occur with serious consequences.

Silent ^{١٢} _٦

Epstein-Barr Virus (EBV)



Clinical findings:

- Incubation period ranges from 4-20 days.
- The triad of fever, sore throat, and lymphadenopathy in a young adults , especially when it is accompanied by lymphocytosis in blood is highly suggestive of I.M.
- Splenomegaly & Hepatitis is frequent.
- Most primary infections in **children** are asymptomatic, however, in **young adults**, the typical illness of acute I.M often develops.
- The typical illness is self-limited and lasts 2-4 weeks.



بخف لحاله

Diagnosis of infectious mononucleosis (IM) due to EBV

1) Hematological criteria:

- During the first few days of the disease, there is **leucopenia** followed by **leucocytosis** (up to 25000/cmm).
- Films show absolute lymphocytosis with presence of **atypical lymphocytes (glandular fever cells)** which appear **large with deep blue foamy cytoplasm and oval or kidney shaped nuclei**.

N.B. Atypical lymphocytes are **cytotoxic T cells** that react against the EBV-infected B cells.



هاي عبارة عن non specific antibodies ، و وجدوا انه اذا حطناها على sheep or horse RBCs رح يصيرلهم agglutination ، و صرنا نستخدم هاي الخاصة في التشخيص

2) Serology :

A) Detection of heterophil antibody:

These **non-specific** antibodies to sheep or horse RBCs present in a high proportion in cases of I.M due to EBV and can be detected by:

- Paul –Bunnell test: tube agglutination test.
- Monospot test: latex agglutination test.

B) *EBV specific serology*:

The IgM VCA (useful for diagnosing acute infection).

The IgG VCA (useful for diagnosing remote infection).

هذا هو الفحص ، و اذا بين خطين يعني النتيجة positive



3) Virus isolation:

EBV can be isolated (**with difficult**) from throat washings in cultures of B lymphocytes.

عن طريق اني ازرع ال B lymphocytes ، لكن طبعا هاي طريقة
صعبة و مش مضطرين نعملها

4) DNA Hybridization:

Detection of EBV in the peripheral B lymphocytes of the patients by DNA hybridization is **the most sensitive method**.

هاي عن طريق اني ادور على ال DNA تاع الفيروس ، عن طريق ال PCR أو ال hybridization و اخذناهم
بالجينتكس

Treatment

- No antiviral therapy is necessary for uncomplicated infectious mononucleosis.
- Acyclovir has little activity against EBV, but administration of high doses may be useful in life-threatening EBV infections.

Prevention

There is **no** available EBV vaccine.

PARVOVIRUS-B19

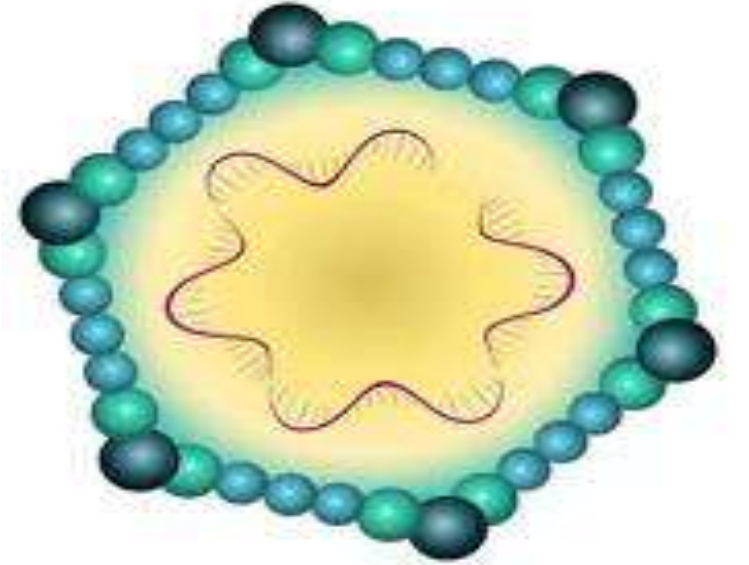


SLAPPED CHEEK
SYNDROME

Classification & Morphology

Belong to Parvoviridae family, Erythrovirus genus.

- **Virion:** very small, 18–26 nm in diameter.
- **Non-enveloped.**
- **Capsid:** icosahedral symmetry.
- **Genome:** Single-stranded DNA.
- **Replication:** In the Nucleus, highly dependent on cellular functions.



ParvoVirus B19

مراجعة ، ما حكته الدكتورة ، بس انا بحب
اتفلسف

حكيانا الفصل الماضي انه كثير صغير وانه complete dependent on cellular function ، و حكيانا انه هو بستنى الخلية تدخل بال S phase of replication ، عشان يتضاعف معها ، اما باقي الفيروسات فهي بتجبر الخلية انها تدخل بال s phase

Pathogenesis

ال B19 targets for human مهمة جدا ، و السلايد
الجاي كمان مهم ، حيث انهم (حتة مهمة أوي للأسئلة)

B19 virus is transmitted by:

- Primarily by the respiratory route.
- Parenterally by blood transfusions or by infected blood products.
- Vertically from mother to fetus (transplacental).

Principal targets for human B19 parvovirus are:

عزم صيغ

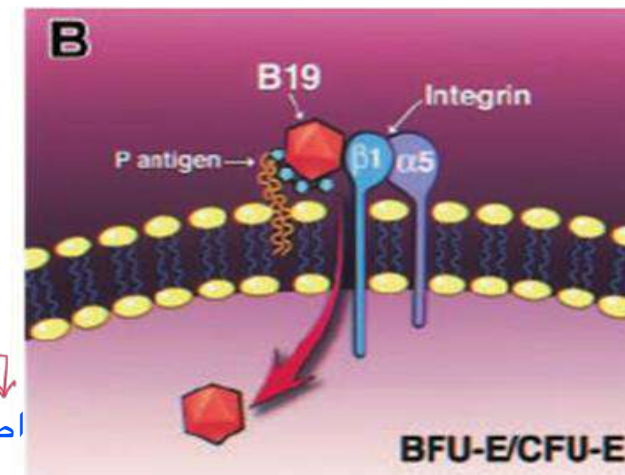
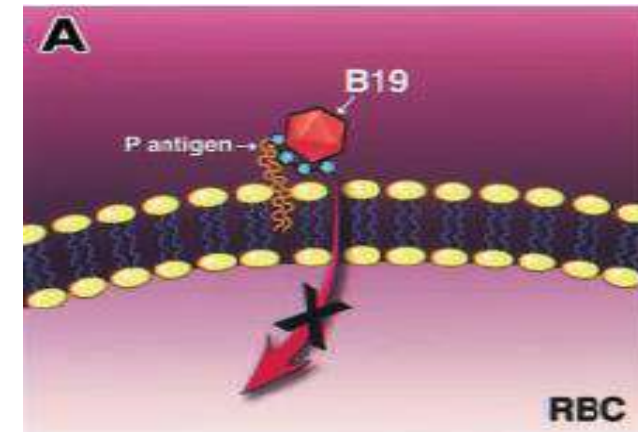
- Red blood cell precursors (erythroblasts): Hence, the major sites of virus replication in patients are the adult bone marrow and the fetal liver.
خقف ← مش ال mature RBC
- Endothelial cells in the blood vessels.

Why B19 virus replicates in red cell precursors but not in mature red cells



- The cellular receptors for B19 are blood group **P antigen** (globoside) & **Integrin** coreceptor.
- Erythroid progenitor cells, express both P antigen and integrin (permissive cell) while mature RBCs express P antigen only (non-permissive cell).
- B19 virus replicates only when a cell is in **S phase** (mature red cells have no nucleus and not divide)

اصلا ال mature RBC فش فيها nucleus



Clinical Findings

1) Erythema Infectiosum (Slapped Cheek Syndrome, Fifth Disease)

- This is a mild disease, primarily of **childhood**, characterized by:
 - Low-grade fever, runny nose (coryza), and sore throat.
 - Red rash that is most prominent on the cheeks.
 - A “lacy,” less intense, erythematous rash appears on the body.
- The symptoms resolve in about 1 week.



في عنا خمس امراض بسببوا rash عند ال infants ، و
المرض يلي شرحناه هو المرض الخامس

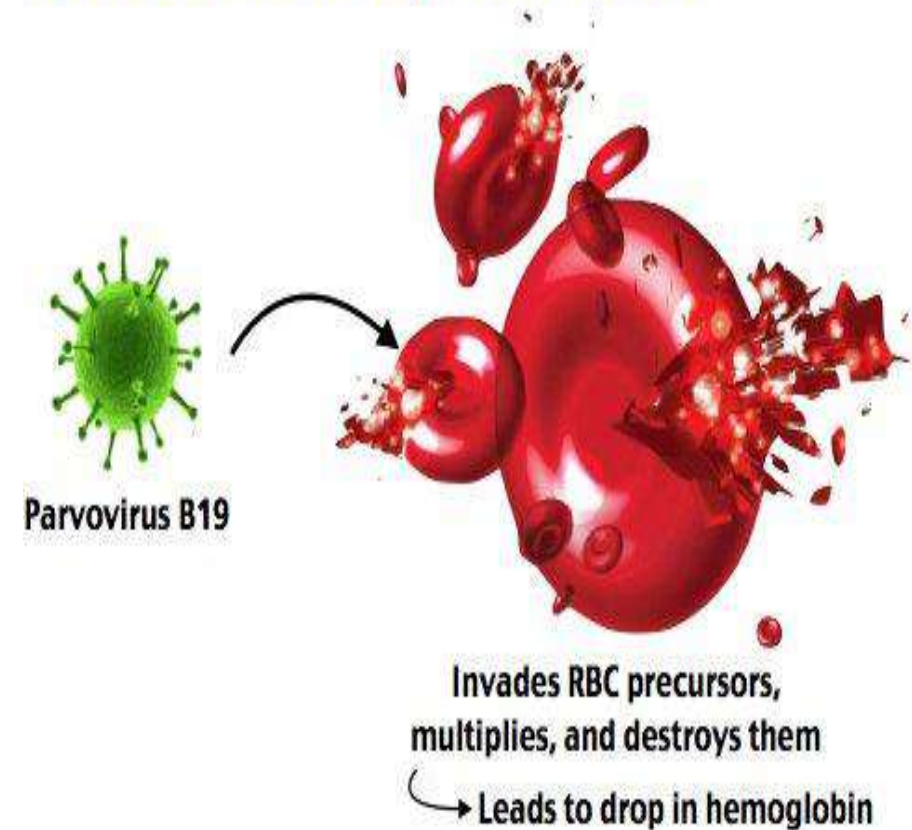
- The disease in children is also called **fifth disease**. The four other maculopapular rash diseases of childhood are **measles**, **rubella**, **scarlet fever**, and **roseola infantum**.
- The **pathogenesis** of rash is based in part to **immune complexes** (composed of virus and IgM or IgG) and in part to **death of infected endothelial cells of the blood vessels**.

وهذا ال complex يترسب على ال endothelial cells
ويعملي vasculitis

2) Aplastic Anemia (Aplastic crisis)

- Parvovirus B19 is the cause of transient and severe aplastic anemia (aplastic crisis) that occur in children with chronic anemia, such as sickle cell anemia and thalassemia.
- The syndrome is an abrupt cessation of red blood cell synthesis in the bone marrow and hence, a rapid worsening of anemia.
- The temporary arrest of production of red blood cells becomes apparent only in patients with chronic hemolytic anemia because of the short life span of their erythrocytes; a 7-day interruption in erythropoiesis would not be expected to cause detectable anemia in a normal person.

Parvovirus B19 Aplastic Crisis



هذا المرض ما بصير عند الانسان الطبيعي ، لانه عمر ال RBC ١٢٠ يوم ، فاذا دخل الفايروس بجسمي و وقف عملية ال erythropoiesis ، لمدة ٧ ايام ، انا ما رح اتأثر ، اما الاشخاص يلي اصلا عندهم مشاكل زي الانيميا و ثلاثيميا و غيرها ، هذول عمر خلايا الدم عندهم تقريبا ١٠ ايام ، فانا اذا وقفت تصنيع الدم و لو لفترة صغيرة ، رح اضر المريض و رح يصير عنده aplastic anemia

3) Fetal Infections (Hydrops fetalis)

- If a woman is infected with B19 virus during the first or second trimester of pregnancy, the virus may cross the placenta and infect the fetus resulting in hydrops fetalis and fetal death.
- Hydrops fetalis manifests as massive edema of the fetus. This is secondary to congestive heart failure precipitated by severe anemia.
- B19 virus is **NOT** a common cause of congenital abnormalities, probably because the fetus dies early in pregnancy.

الجنين بموت ، سواء قبل
الولادة ، او بعد الولادة



4) Arthritis

Parvovirus B19 infection in **adults**, especially women, can cause arthritis mainly involving the small joints of the hands and feet bilaterally. It resembles rheumatoid arthritis (**immune complex–related arthritis**).

5) Chronic B19 Infection

People with **immunodeficiencies**, especially HIV-infected, chemotherapy, or transplant patients, can have **chronic anemia**, **leukopenia**, or **thrombocytopenia** as a result of chronic B19 infection.

Laboratory Diagnosis

- Detection of viral DNA by PCR is **the most sensitive** tests.
B19 DNA has been detected in serum, blood cells, amniotic fluid, and respiratory secretions.
- Virus isolation **is not used to detect infection as the virus is difficult to grow.** ↪ It is not practical
- **Serology by detecting IgM antibodies.**
In immunocompromised patients, **antibodies may not be detectable;** therefore, **viral DNA in the blood can be assayed by PCR methods.**

Treatment & Prevention

- No vaccine available. Self limiting
- There is no specific treatment for B19 infection. Pooled immunoglobulins may have a beneficial effect on chronic B19 infection in patients with immunodeficiencies.

خالص التحيات للدكتورة هالة طبل
و لجمهورية مصر العربية



Thank
you

