HLS

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MICROBIOLOGY

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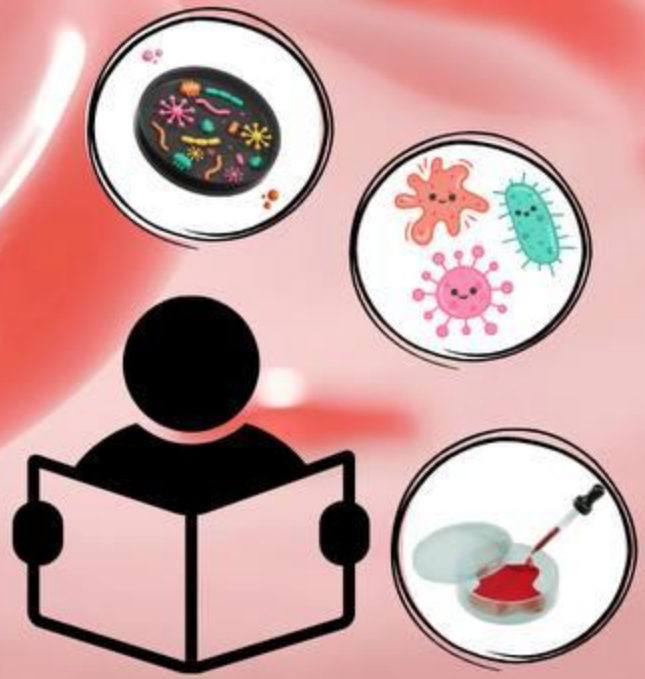


Viral Diseases in the Hematolymphatics

Color code

- Slides
- Doctor
- Additional info
- Important

By:Ass. Prof. Nader Alaridah

- In this lecture, we are going to discuss 4 types of viruses, which are: parvoviruses (affect erthrocytes) , herpes simplex viruses, Epstein Barr virus (B cells) , and Human T lymphotropic viruses.
- It is important to know the target cell for each virus.

Parvoviruses

- Members of the family Parvoviridae, are small (diameter, ~22 nm), nonenveloped, icosahedral viruses with a linear single-strand DNA genome of ~5000 nucleotides.
- These viruses are dependent on either rapidly dividing host cells or helper viruses for replication.
- This group's only human pathogen, parvovirus B19, is the causative virus in erythema infectiosum (also known as "slapped cheek syndrome" or the "fifth disease") in children and causes aplastic crisis in anemic patients.
- The virus also contributes to joint diseases, embryopathies, and tissue rejection following renal transplants.

• Parvovirus infects the RBCs progenitors.
• Remember, a person may become infected without developing a disease (Asymptomatic) or may develop disease after infection.

• Most of the infected patients by paravirus are asymptomatic, the clinical symptoms depend on the underlying conditions, when children get infected with parvovirus, they will develop erythema infectiosum (slapped cheek syndrome) or it is called "Fifth disease".

• But when it affects individuals with underlying conditions (ex:hemolytic anemia), this parvovirus will aggravate this anemia leading to clinical entity called transient aplastic crisis, why is it called transient? Till to the end of the cytopathic effect of the parvovirus infection (temporary).

• If immunodeficient individuals are infected, they will develop a pure red cell aplasia.

• If the virus transmits vertically (from mother to fetus), it leads to hydrops fetalis, the severity of the outcome on the fetus depends on when he got infected, if the infection takes place in the first trimester it usually leads to fetal loss, in the second trimester infection, hydrops fetalis develops and as a consequence fetal loss can occur, in the third trimester infection, usually harmless.

•The distribution and effects of parvovirus B19 infection vary significantly depending on a person's age and underlying health conditions.

TABLE 31-1 Important Properties of Parvoviruses

Virion: Icosahedral, 18–26 nm in diameter, 32 capsomeres
Composition: DNA (20%), protein (80%)
Genome: Single-stranded DNA, linear, 5.6 kb, MW 1.5–2.0 million
Proteins: One major (VP2) and one minor (VP1)
Envelope: None
Replication: Nucleus, dependent on functions of dividing host cells
Outstanding characteristics: Very simple viruses Human pathogen, B19, has tropism for red blood cell progenitors One genus contains viruses that are replication-defective and require a helper virus

Parvovirus B19

- The parvoviruses are among the smallest viruses with a diameter of 19–25mm.
- They are icosahedral, nonenveloped, and their genome is in the form of single-stranded DNA (ssDNA).
- Some parvoviruses can only replicate in the presence of a helper virus (adenovirus or herpesvirus).
- Parvovirus B19, the only human pathogenic parvovirus identified to date, is capable of autonomic replication, i.e., it requires no helper virus.

- Other species, distinct from parvoviruses, are referred to as dependoviruses because they rely on other viruses for their replication).

Epidemiology.

- The B19 virus is widespread. Infections can occur throughout the year in all age groups and as outbreaks or as sporadic cases.
- Infections are most commonly seen as outbreaks in schools
- Droplet infection or the fecal-oral route, analogous to other parvoviruses, is suspected. Blood and blood products are infectious, so that multiple transfusion patients and drug addicts are high incidence groups. (Droplet infection is the main transmission route).

Pathogenesis

- Parvovirus B19 replicates in the bone marrow in erythrocyte precursor cells, which are destroyed in the process.
- In patients already suffering from anemia (sickle-cell anemia, chronic hemolytic anemia), such infections result in so-called aplastic crises in which the lack of erythrocyte resupply leads to a critical shortage.
- The virus also appears to cause spontaneous abortions in early pregnancy and fetal damage in late pregnancy (hydrops fetalis).
- In otherwise healthy persons, these infections usually run an asymptomatic course. They can, however, also cause a harmless epidemic infection in children, erythema infectiosum (“slapped-cheek syndrome” or “fifth disease”).

• Parvovirus B19 replicates in the bone marrow in erythrocyte precursor cells, which are destroyed in the process.
• Parvovirus receptor is found in erythrocyte precursor mainly and endothelial cells, this receptor is called P antigen (also known as globoside).
• It also has a receptor on the mature RBCs but remember they are not dividing cells so it won't induce any effect on them, all precursor ells care susceptible to be infected.
• When the endothelial cells get infected, the body responds by producing antibodies against viral particles forming immune complexes which can deposits in different parts of the body producing erythema infectiosum.

• In the table , here is the 4 entities of parvovirus disease, don't forget that the majority are asymptomatic.
• In erythema infectiosum, symptomatic people (adults) are presented mainly with arthalgia-arthritis or polyarthropathy syndrome, the clinical presentation is age-dependent.

- Cutaneous rash in pediatric patients:
1st: measles
2nd : rubella
3rd:scarlet fever
4th: roseolla infantum
5th: Erythema infectiosum

TABLE 31-2 Human Diseases Associated with B19 Parvovirus

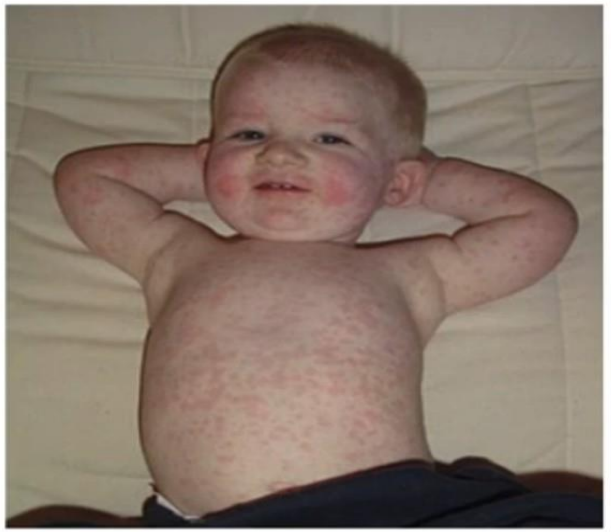
Syndrome	Host or Condition	Clinical Features
Erythema infectiosum	Children (fifth disease)	Cutaneous rash
	Adults	Arthralgia-arthritis
Transient aplastic crisis	Underlying hemolysis	Severe acute anemia
Pure red cell aplasia	Immunodeficiencies	Chronic anemia
Hydrops fetalis	Fetus	Fatal anemia

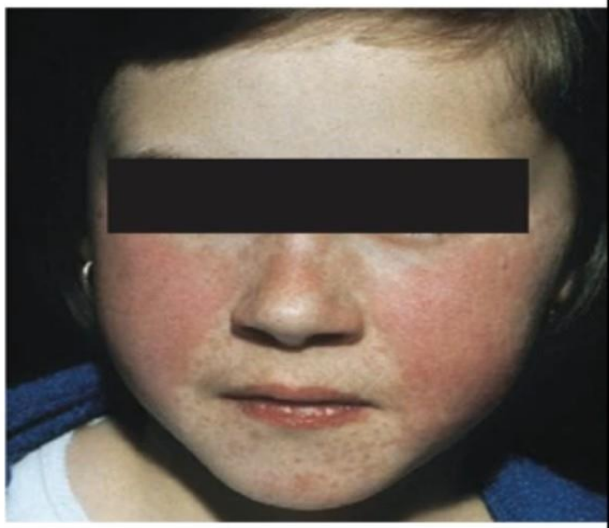
Not teratogenic خلي ببالك انه هذا الفيروس

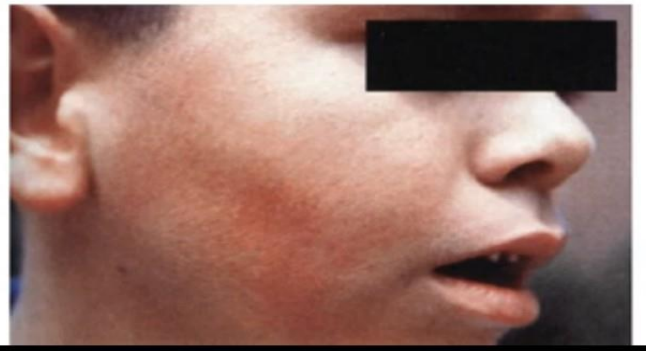
CLINICAL MANIFESTATIONS

❖ Erythema Infectiosum (Fifth disease or slapped-cheek disease)

- Infection begins with a minor febrile prodrome ~7–10 days after exposure.
- the classic facial rash develops several days later; after 2–3 days, the erythematous macular rash may spread to the extremities in a lacy reticular pattern.
- Adults typically do not exhibit the “slapped-cheek” phenomenon but present with arthralgia, with or without the macular rash.

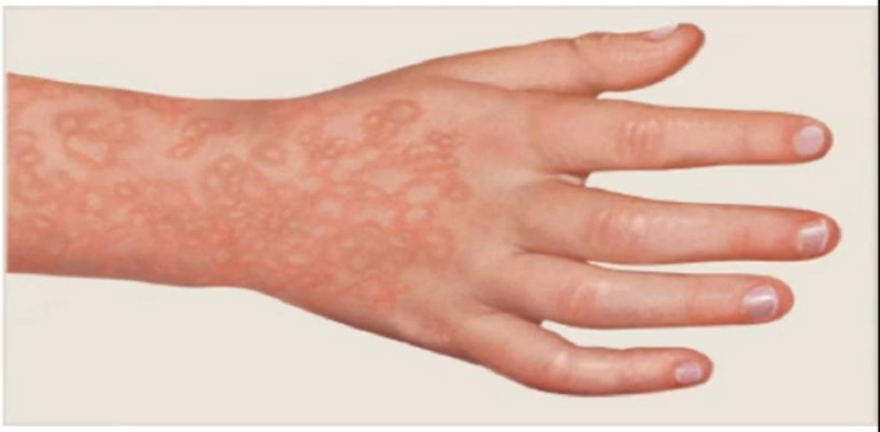






❖Polyarthropathy Syndrome

- Although uncommon among children, arthropathy occurs in ~50% of adults and is more common among women than among men.
- The distribution of the affected joints is often symmetrical, with arthralgia affecting the small joints of the hands and occasionally the ankles, knees, and wrists.
- Resolution usually occurs within a few weeks, but recurring symptoms can continue for months.



•Erythema Infectiosum

• The erythema in their faces are represented as reticular or lacy shape in apperance.
• Before rash onset, there is a period of febrile prodrome occurring 7-10 days before rash onset.
• After face involvement, rash spreads out to the trunk (maculopapular rash is a type of skin rash characterized by both macules and papules. Macules are flat, discolored spots on the skin, often red or pink but Papules are small, raised bumps, which can also be red or pink).
• They also may have arthalgia-arthritis.

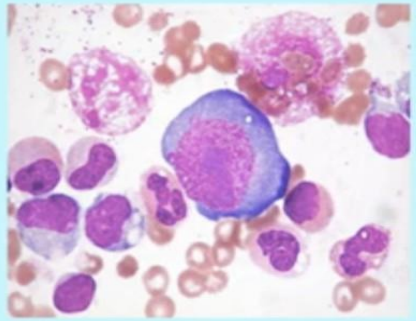
•Polyarthropathy Syndrome

•The clinical presentation of adults typically is: pain, swelling of the small hand joints, ankle, feet (symmetrical), to a lesser extent, they may develop rash but it is more common and classic in children.
• Polyarthropathy Syndrome refers to a condition characterized by inflammation and pain in multiple joints, which resembles juvenile rheumatoid arthritis (JRA), now commonly referred to as juvenile idiopathic arthritis (JIA) and If you measure the rheumatoid factor, you will find high levels.

❖Transient Aplastic Crisis (TAC):

- In most individuals with B19V infection, asymptomatic transient reticulocytopenia occurs.
- However, in patients who depend on continual rapid production of red cells, infection can cause transient aplastic crisis. Affected individuals include those with hemolytic disorders, hemoglobinopathies, red cell enzymopathies, and autoimmune hemolytic anemias.
- Patients present with symptoms of severe anemia (sometimes life-threatening) and a low reticulocyte count, and bone marrow examination reveals an absence of erythroid precursors and characteristic giant pronormoblasts.

Giant pronormoblast is parvovirus infection



- reveals an absence of erythroid precursors (since they are got infected by the virus).

- If the underlying condition was chronic anemia because the patient is immunodeficient for any reason (congenital or acquired), and the infection takes place, in this state, it is called pure red cell aplasia.

❖Pure Red-Cell Aplasia/Chronic Anemia (almost persistent not transient)

- Chronic B19V infection has been reported in a wide range of immunosuppressed patients, including those with congenital immunodeficiency, AIDS, lymphoproliferative disorders (especially acute lymphocytic leukemia), and transplantation.

- Patients have persistent anemia with reticulocytopenia, absent or low levels of B19V IgG, high titers of B19V DNA in serum, and—in many cases—scattered giant pronormoblasts in bone marrow.

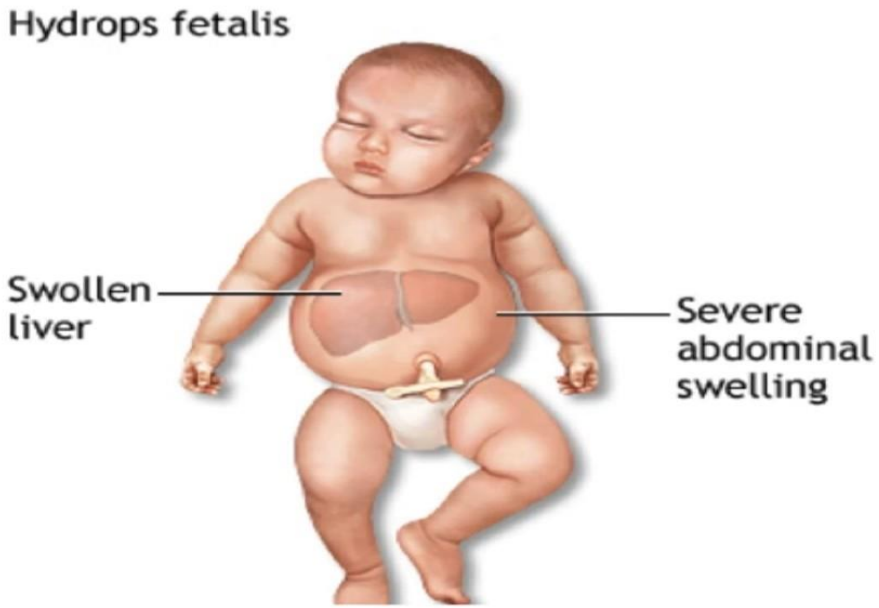
- Patients have absent or low levels of B19V IgG, IgM (since they are already immunodeficient)

• If individuals experiencing a transient aplastic crisis due to parvovirus infection suffer a more pronounced impact on their existing anemia, they may derive substantial benefits from receiving a blood transfusion, depending on the severity or threshold of their anemia, while patients experiencing pure red cell aplasia, blood transfusion and immunoglobulins (IV) should be administered, the disease (pure red cell aplasia) could persist after receiving the therapy.

❖Hydrops Fetalis

- B19 infection during pregnancy can lead to hydrops fetalis and/or fetal loss.

- The risk of transplacental fetal infection is ~30%, and the risk of fetal loss (predominantly early in the second trimester) is ~9%. Although B19V does not appear to be teratogenic



• Hydrops fetalis is characterized by abnormal swelling of the abdomen, as we said parvovirus infect progenitor RBCs and destruct them leading to severe anemia, the heart overload increase trying to compensate the condition, leading to accumulation of the fluids in different part, this condition is not caused by the teratogenic properties of the virus, instead it arises due to the virus impact on the RBCs.

• Intra-uterine fetal blood transfusion revolutionized the treatment of these affected fetuses after diagnosis of immune fetal hydrops.

Diagnosis.

- An enzyme immunoassay reveals antibodies of the IgG and IgM classes.
- Remember that, in pure red cell aplasia, lower levels of antibodies are observed or absent
- During the viremic phase, at the onset of clinical symptoms, the virus can also be identified in the blood by means of electron microscopy or PCR.

- In-vitro culturing of the pathogen is not standard procedure.

Treatment

- Symptomatic treatment. (Children could be treated by anti-histamine and anti- pyretics).
- TAC precipitated by B19V infection frequently necessitates symptom-based treatment with blood transfusions.
- Commercial immune globulin (IVIg) from healthy blood donors can cure or ameliorate persistent B19V infection in immunosuppressed patients.
- Administration of IVIg is not beneficial for erythema infectiosum or B19V-associated polyarthropathy. Intrauterine blood transfusion can prevent fetal loss in some cases of fetal hydrops.
- There is no vaccine against human parvovirus

Herpesviruses

- The viruses in this family all feature a practically identical morphology, but show little uniformity when it comes to their biology and the clinical pictures resulting from infections.

- One thing shared by all herpesviruses is the ability to reactivate after a period of latency.

- The herpes simplex virus (HSV, two serotypes), The varicella-zoster virus (VZV), Cytomegalovirus (CMV), The **Epstein-Barr virus (EBV),** Human herpesvirus 6 (HHV 6) and **Human herpesvirus 8 (HHV 8).**

- Herpes viruses possess a double-stranded DNA genome (VS single-stranded DNA genome of Parvovirus B19).
- Two important features to keep in mind regarding herpes viruses:
- 1- Their contamination (carriage) rate is high (when searching for herpes antigens or antibodies directed against those antigens, a high seroprevalence is noted).
- 2- They tend to establish latency (They stay dormant in our body and get reactivated later on).
- The two serotypes of HSV are HSV-1 (Herpes labialis virus) and HSV-2 (Herpes genitalis virus).
- Varicella-zoster virus (HHV 3) causes chickenpox in children (primary infection) and zoster in adults (upon reactivation).
- Epstein-Barr virus (HHV 4) causes infectious mononucleosis (kissing disease; since it is primarily transmitted through salivary secretions) that is common among college students. It has been found that EBV is associated with different malignancies.
- Cytomegalovirus (HHV 5) causes fatal systemic infections, especially in immunocompromised patients.
- HHV 6 causes exanthema subitum (Roseola infantum).
- HHV 8 is also called Kaposi sarcoma associated herpes virus.

Herpesviruses

- They have dsDNA genomes. Replication of the DNA and the morphogenesis of the virus particle take place in the host-cell nucleus.

- The envelope (inner nuclear membrane) is then formed when the virus penetrates the nuclear membrane.

- Common to all herpesviruses is a high level of generalized contamination (60–90% carriers) and the ability to persist in a latent state in the body over long periods.

Epstein-Barr virus (EBV)

- The virus is a member of the family Herpesviridae
- Is the cause of heterophile-positive infectious mononucleosis (IM), which is characterized by fever, sore throat, lymphadenopathy, and atypical lymphocytosis.
- EBV is also associated with several tumors, including nasopharyngeal and gastric carcinoma, Burkitt's lymphoma, Hodgkin's disease, and (in patients with immunodeficiencies) B cell lymphoma.
- The two types of EBV that are widely prevalent in nature are not distinguishable by conventional serologic tests.

EBV also causes oral hairy leukoplakia.
Gastric carcinoma is the most common tumor caused by EBV worldwide.

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. In lower socioeconomic groups and in areas of the world with deficient standards of hygiene (e.g., developing regions), EBV tends to infect children at an early age, and IM is uncommon.
- In areas with higher standards of hygiene, infection with EBV is often delayed until adulthood, and IM is more prevalent.

- The distribution of EBV infections is bimodal (two peaks). The first peak occurs in early childhood (especially in developing countries due to poor hygiene standards) where patients come with pharyngitis, with/without tonsilitis. The second peak occurs in late adolescence where patients present with typical features of infectious mononucleosis.

- EBV receptor is CD21 (complement receptor to C3d component).

TRANSMISSION

- 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 less intimate contact is rare. 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. Shedding is increased in immunocompromised patients and those with IM.

The most common route of transmission is salivary secretions.
It can be transmitted through blood transfusion (from infective donor to a recipient), vertical transmission (mother to fetus), and sharing syringes or needles.

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. While B cells may become infected after contact with epithelial cells.
- The virus then spreads through the bloodstream. The proliferation and expansion of EBV-infected B cells along with reactive T cells result in enlargement of lymphoid tissue. Polyclonal activation of B cells leads to the production of antibodies to host-cell and viral proteins.
- This virus also persists in latency, probably for the life of the patient, in (immortalized) B cells.
- If T cell immunity is compromised, EBV-infected B cells may begin to proliferate , virus-induced proliferation is but one step in a multistep process of neoplastic transformation.

- EBV infects B cells.
- Because EBV is transmitted through saliva, it gets access to the epithelium lining the oropharynx and nasopharynx initiating an inflammatory response (pharyngitis). Later on, B and T lymphocytes reach sites of infection where EBV can infect B cells through CD21 (CR2) receptor. Once inside the B cell, EBV binds a promoter region causing persistent activation of C-MYC protooncogene expression, and therefore uncontrolled proliferation of B cells (even T cells can not control that growth). This is why EBV is associated with different cancers.
- When B cells return to lymph nodes, they cause proliferation of T cells in the paracortex leading to lymphadenopathy (enlarged lymph node).

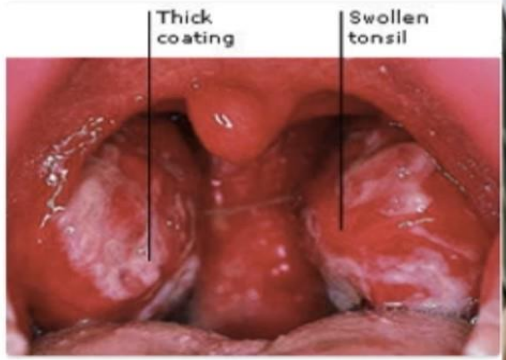
- The EBV receptor (CD21) on the surface of B cells is also the receptor for the C3d component of complement.

- During latent infection of B cells, only the EBV nuclear antigens (EBNAs), latent membrane proteins (LMPs), and small EBV RNAs (EBERs) are expressed in vitro.

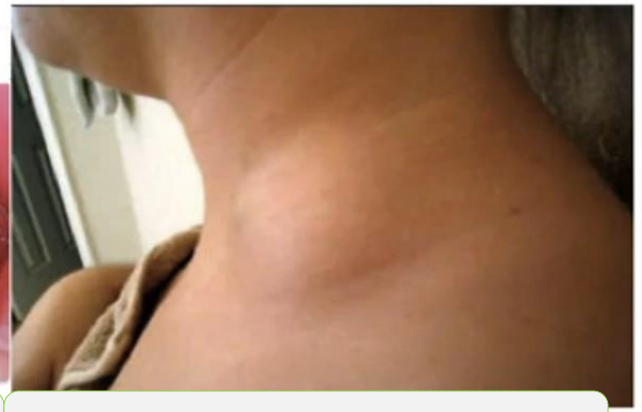
These antigens are of great significance in diagnosing EBV infection.

- EBV-transformed B cells secrete immunoglobulin; only a small fraction of these cells produce virus.

CLINICAL MANIFESTATIONS



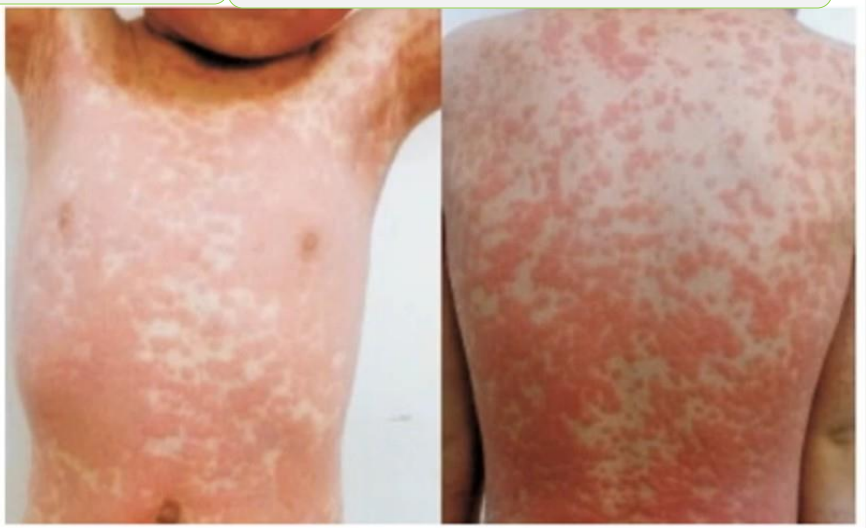
Pharyngitis with tonsilitis.



Cervical lymphadenopathy.

❖Infectious mononucleosis (IM)

- The incubation period for IM in young adults is ~4–6 weeks. A prodrome of fatigue, malaise, and myalgia before the onset of fever, sore throat, and rash, lymphadenopathy.
- fever, fatigue, myalgia, and malaise,pharyngitis, lymphadenopathy, splenomegaly, and atypical lymphocytes
- Liver and spleen involvement and enlargement



The rash appears in response to deposition of immune complexes.

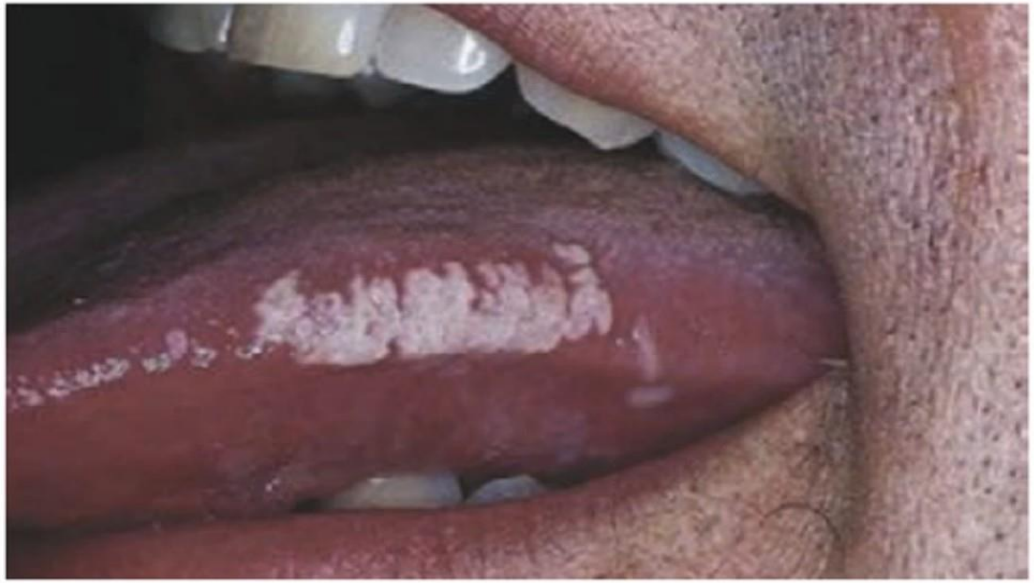
Morbilliform rash starts on the trunk and then spreads to the extremities (centrifugal pattern).

EBV-Associated Diseases Other Than IM

Atypical lymphocytes (especially B cells) appear in peripheral blood smear.

- B cell hyperplasia or poly- or monoclonal lymphoma.
- X-linked lymphoproliferative disease
- Oral hairy leukoplakia
- Burkitt's lymphoma
- Anaplastic nasopharyngeal carcinoma
- Gastric carcinoma.
- Hodgkin's disease

It causes Hodgkin's and non-Hodgkin's lymphoma.



➢ There are characteristic chromosome translocations that involve immunoglobulin genes and result in deregulation of expression of the c-myc proto-oncogene .

This is oral hairy leukoplakia.
It is a benign condition that takes place in AIDS patients when infected with EBV.

DIAGNOSIS

➢Molecular Assays for Identification of Virus

- Nucleic acid hybridization is the most sensitive means of detecting EBV in patient materials.

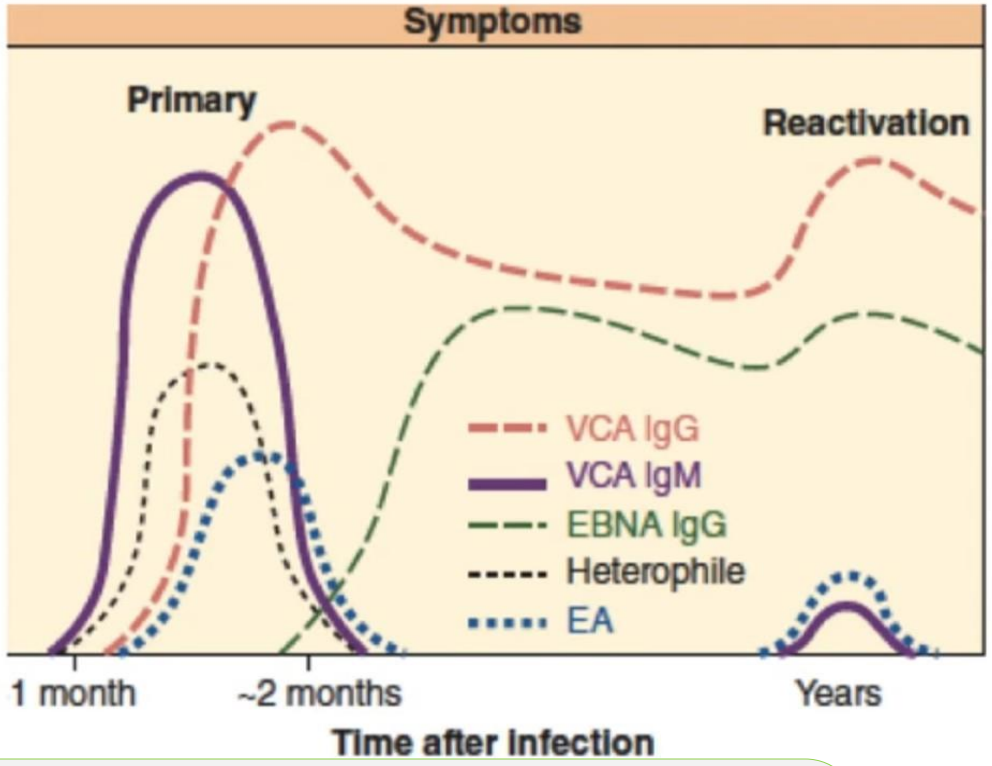
➢ Isolation of Virus

- EBV can be isolated from saliva, peripheral blood, or lymphoid tissue by immortalization of normal human lymphocytes, usually obtained from umbilical cord blood.

The most commonly used method for diagnosis of infectious mononucleosis is serology.
IgM antibodies against VCA are produced within a month, reaching a peak and then dropping down within two months and a half. (When testing for infectious mononucleosis we look for IgM antibodies).
IgG antibodies against VCA appear after IgM antibodies and persist throughout life.

➢ Serology

- Enzyme-linked immunosorbent assays, immunoblot assays, and indirect immunofluorescence tests using EBV-positive lymphoid cells.
- The heterophil agglutination test (Monospot)



Mononucleosis --> Monospot.
The basis for monospot test is mixing the patient's serum with animal blood (hence the name, heterophile).
If the patient's serum has antibodies against EBV, RBCs will agglutinate (positive monospot test).
It is used as a confirmatory test supporting the diagnosis of infectious mononucleosis.
It is a non-specific test.

TREATMENT

- Acyclovir reduces EBV shedding from the oropharynx during the period of drug administration, but it does not affect the number of EBV-immortalized B cells.

- Acyclovir has no effect on the symptoms of mononucleosis and is of no proved benefit in the treatment of EBV-associated lymphomas in immunocompromised patients .

- There is no EBV vaccine available.

Acyclovir is given to prevent the transmission cycle by reducing viral shedding through salivary secretions. It does not reduce the severity of symptoms, duration of symptoms and sequelae (development of cancer).

HUMAN HERPESVIRUS 8

- A new herpesvirus, designated HHV-8 and also called KSHV, was first detected in 1994 in Kaposi sarcoma specimens .
- KSHV is lymphotropic and is more closely related to EBV
- The KSHV genome (~165 kbp) contains numerous genes related to cellular regulatory genes involved in cell proliferation, apoptosis, and host responses (cyclin D, cytokines, chemokine receptor) that presumably contribute to viral pathogenesis.
- KSHV is the cause of Kaposi sarcomas, vascular tumors of mixed cellular composition, and is involved in the pathogenesis of body cavity-based lymphomas occurring in AIDS patients.

This is called molecular piracy.

The pathogenesis is still unclear.

TRANSMISSION

- Contact with oral secretions is likely the most common route of transmission.

- The virus can also be transmitted sexually, vertically, by blood, and through organ transplants. Viral DNA has also been detected in breast milk samples in Africa.

Breast milk is also a documented route of transmission for HTLV-1. Lactating mothers are told not to breastfeed their babies.

DIAGNOSIS

- Viral DNA can be detected in patient specimens using PCR assays.
- Direct virus culture is difficult and impractical.
- Serologic assays are available to measure persistent antibody to KSHV using indirect immunofluorescence, Western blot, and enzyme-linked immunosorbent assay formats.

TREATMENT

- Foscarnet, famciclovir, ganciclovir, and cidofovir have activity against KSHV replication.

Human T-Lymphotropic Viruses

- HTLV-1 has been established as the causative agent of adult T-cell leukemia-lymphomas (ATL) as well as a nervous system degenerative disorder called tropical spastic paraparesis; HTLV-1-associated myelopathy (HAM).

- The human lymphotropic viruses have a marked affinity for mature T cells. Specifically CD4 T cells.

- The virus is distributed worldwide, with an estimated 20 million infected individuals.

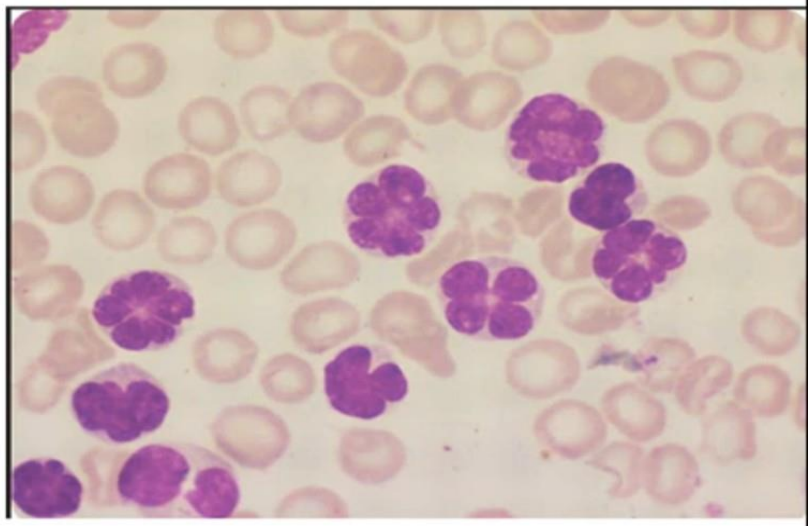
HTLV-1 is an RNA oncogenic virus that belongs to the same family as HIV (retroviridae).
ATL is one of the most aggressive tumors affecting human beings (one-year survival when diagnosis is established is less than 5%).
HAM destroys myelin sheath in a manner that resembles multiple sclerosis.

TRANSMISSION

- Transmission of HTLV-1 seems to involve cell-associated virus.
- Mother-to-child transmission via breast feeding is an important mode.
- Blood transfusion is an effective means of transmission, as are sharing blood contaminated needles (drug abusers) and sexual intercourse.
- There is a long latency period (≈30 years) before the onset of leukemia.

Human T-lymphotropic virus **Clinical Syndromes**

- HTLV infection is usually asymptomatic but can progress to ATLL in approximately 1 in 20 persons over a 30 years old.
- ATLL caused by HTLV-1 is a neoplasia of the CD4 helper T cells that can be acute or chronic .
- The malignant cells have been termed “flower cells” because they are pleomorphic and contain lobulated nuclei. This is pathognomonic of HTLV-1.
- ATLL is usually fatal within a year of diagnosis, regardless of treatment



DIAGNOSIS

- Serology ELISA , Western blot
- Viral PCR

TREATMENT

- For the small number of patients who develop HTLV-1-related disease, therapies are not curative.

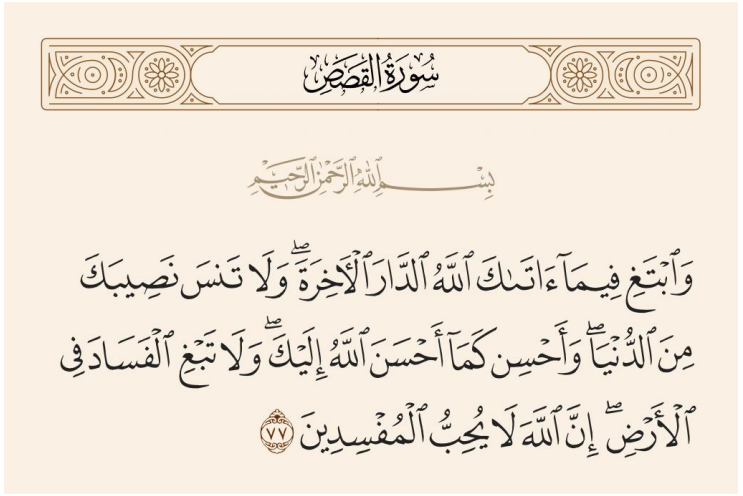
- No specific antiviral therapy However, the combination of interferon α and zidovudine may extend survival

PREVENTION

- Women in endemic areas should not breast-feed their children, and blood donors should be screened for serum antibodies to HTLV-1.
- As in the prevention of HIV infection, the practice of safe sex and the avoidance of needle sharing are important.

❑ Additional sources

1. Parovirus (very useful video)



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V1→ V2			
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