Doctor.021

no.??

HLS MICROBIOLOGY

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Hello there, in this sheet, we are going to discuss 4 types of viruses, which are: parvoviruses, herpes simplex viruses, Epstein Barr virus, and Human T lymphotropic viruses.

- **what is mentioned in slides is written in red**
- **doctor's notes are written in black**
- **the parvoviruses are among the smallest viruses with a diameter 19-25mm**
- **They are icosahedral, non-enveloped, and their genome is in the form of single - stranded DNA (ssDNA)**
- **icosahedral shape is composed of equilateral triangles, each triangle is composed of protein subunit.**

Some parvoviruses can only replicate in the presence of a helper viruses (ex: adenoviruses, herpes viruses)

Parvovirus B19, the only human pathogenic parvovirus identified to date, is capable of autonomous replication, ie., it requires no helper viruses.

- **Parvoviruses, also known as erythroparvovirus, rely on replicating cells for their replication process, which takes place within the cell's nucleus.**

Other species, distinct from parvoviruses, are referred to as dependo-viruses because they rely on other viruses for their 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

- **Parvovirus infects the RBCs progenitors.**
- **Most of the infected patients are asymptomatic, the clinical symptoms depend on the underlying conditions, when children get infected with parvovirus, they will develop erythema infectiosum (slapped cheek syndrome), 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.**

- **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.**

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

- **What is the difference between the major protein (vp2) and the minor protein (vp1)? Vp2 plays a role in the stability and the infectivity of the particle while vp1 facilitates the attachment and the entry of the virus**

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 is the main transmission route 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

PATHOGENESIS:

• 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 progenitors are 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 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")

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

- In the table above, 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

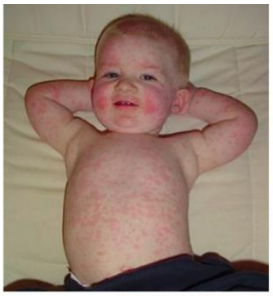
CLINICAL MANIFESTATIONS

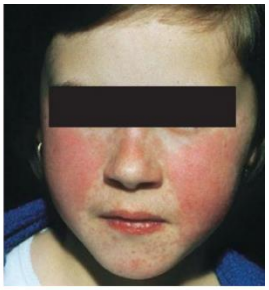
❖ **Erythema Infectiosum (Fifth disease or slapped-cheek disease)**

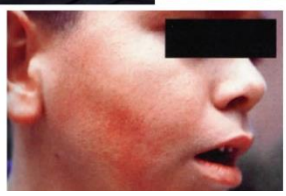
•Infection begins with a minor febrile prodrome ~7–10 days after exposure.

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.**
- **They also may have arthalgia-arthritis**

•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**

- **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**

If u measure the rheumatoid factor, you will find high levels

•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

❖**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 (since they are got infected by the virus) and characteristic giant pronormoblasts.

- 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

• 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, IgM (since they are already immunodeficient), high titers of B19V DNA in serum, and—in many cases—scattered giant pronormoblasts in bone marrow.

- 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

- They have double-stranded DNA
- They are characterized by two features, they all have high contamination rate (or infected rate which is the susceptibility of spreading the pathogen form infected to non-infected person) and latency (being dormant to a period of time and then reactivated again

• 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 -labialis and genitalis), The varicella-zoster virus (VZV) which causes chicken box in children and zoster in adults, Cytomegalovirus (CMV), The Epstein-Barr virus (EBV), Human herpesvirus 6 (HHV 6) and Human herpesvirus 8 (HHV 8).

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, oral hairy leukoplakia

- The most common tumor associated with EPV is gastric carcinoma

• The two types of EBV that are widely prevalent in nature are not distinguishable by conventional serologic tests

EPIDEMIOLOGY

- **It has bimodal distribution: refers to its ability to infect two distinct age groups: children and adolescents or young adults.**

  Children: Primary Infection Phase: In the initial phase, children are often infected with EBV. This primary infection can result in symptoms like pharyngitis (sore throat) with or without tonsillitis

- **Adolescents/Young Adults (Colleague Students): Secondary Infection Phase (More Common Presentation in Europe): The second phase involves the infection of adolescents or young adults, typically within the setting of colleges or among students. This phase is often associated with the more pronounced manifestation of symptoms, which is known as infectious mononucleosis (IM) or the "kissing disease."**

- **EBV receptor is CD21 which is a complement receptor, which interacts specifically with C3d, a fragment of C3 complement protein, it plays an important role in the pathogenesis of the disease.**

• 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.

TRANSMISSION

• EBV is spread by contact with oral secretions (this is why it is called kissing disease). 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

- **Vertical transmission and sharing syringes needles are also routes of transmission.**

• More than 90% of asymptomatic seropositive individuals shed the virus in oropharyngeal secretions(they continue the transmission cycle in the society). Shedding is increased in immunocompromised patients and those with IM.

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.

- B cells is the main target of EBV, when EBV enters the oral cavity through close contact such as kissing, it gets the access into oropharyngeal and nasopharyngeal ET layers establishing its primary infection, then infects B cells by binding to its receptor on the surface of B cell (cd21), once it becomes inside the cell, it will starts its activation cycle using the B cells DNA, leading to an increased number of virus-containing B cells, that triggers the activation of T cells, which recognize the infected B cells as foreign and launch an attack against them.

• 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

- The virus has the ability to attach to cellular promoters, allowing it to persist actively within the cells. When the immune response, particularly from T cells, is weakened or compromised, there's a lack of defense against the virus. This scenario provides an opportunity for the virus to proceed with its neoplastic transformation → immortalization (الخلود)
- Certain B cells that have been infected with the virus circulate toward nearby lymph nodes, once there, they undergo proliferation leading to increased number of the B cells contributing to enlargement of the 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.

- During the infection of EBV, there are some antigens (ex: viral capsule antigen, EBNAs...), and antibodies produced against them, they are used for the diagnosis

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

CLINICAL MANIFESTATIONS

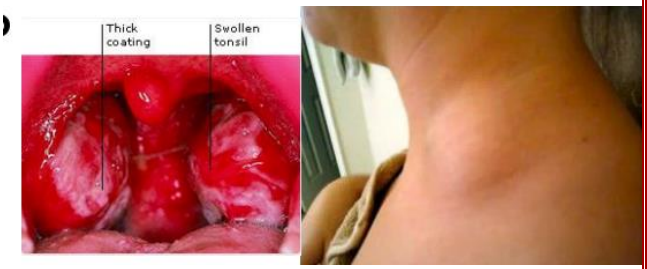
❖Infectious mononucleosis (IM), As previously discussed, the clinical presentation of infectious mononucleosis (IM) is typically observed in adults.

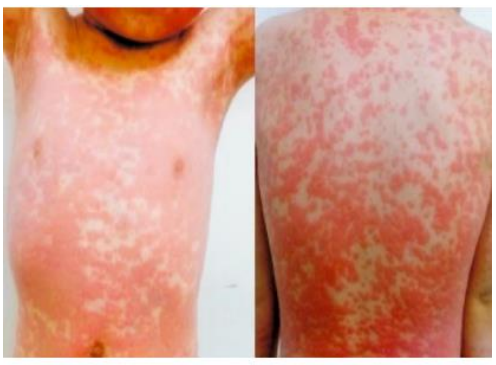
• The incubation period for IM in young adults is ~4–6 weeks. A prodrome of fatigue, malaise, and myalgia before the onset of fever, sore throat, and rash (due to the forming of immune complexes and their deposits), lymphadenopathy.

•fever, fatigue, myalgia, and malaise, pharyngitis, lymphadenopathy, splenomegaly, and atypical lymphocytes

• Liver and spleen involvement and enlargement

- The morbilliform rash that develops in infectious mononucleosis typically begins on the trunk, in contrast to the rash seen in Parvovirus B19, which usually starts on the face.



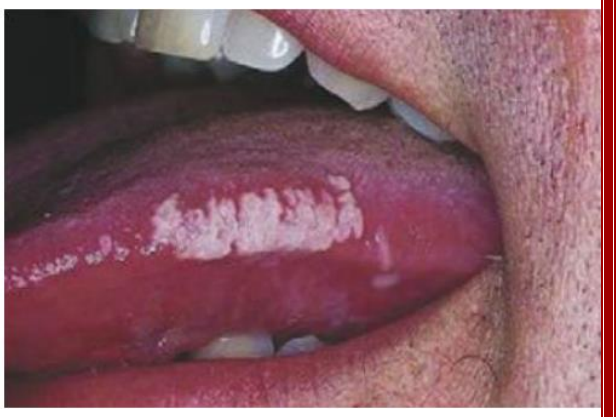


EBV-ASSOCIATED DISEASES OTHER THAN IM:

• B cell hyperplasia or poly- or monoclonal lymphoma.

• X-linked lymphoproliferative disease

- Oral hairy leukoplakia (in the picture)
- Burkitt's lymphoma
- Anaplastic nasopharyngeal carcinoma
- Gastric carcinoma.
- Hodgkin's disease



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

DIAGNOSIS:

- Molecular Assays for Identification of Virus

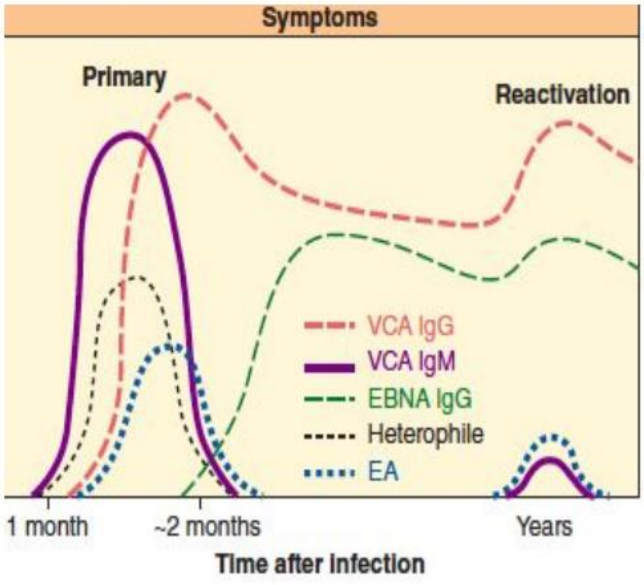
- Nucleic acid hybridization is the most sensitive means of detecting EBV in patient materials.

- 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

SEROLOGY (MOST COMMON USED METHOD)

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



- patient's serum is mixed with animal blood, leading to the development of antibodies that react with the

foreign blood cells causing agglutination (confirmatory test) (commonly used).

- Notice that: VCA IgM is raised almost in three days from the onset of symptoms, reaching its peak in 1.5 month, then it drops significantly.
- VCA IgG is raised after VCA IgM, but it stays persistent.
- EBNA IgG starts appearing late (after 2 months), then it stays positive
- EA (early antigen) appear directly after VCA IgM AND VCA IgG, then drops after VCA IgM.

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 cut the transmission cycle, to reduce the shedding from the respiratory or the salivary secretions.

HUMAN HERPESVIRUS 8:

•A new herpesvirus, designated HHV-8 and also called KSHV, was first detected in 1994 in Kaposi sarcoma specimens.

- It is double-stranded DNA virus
- Kaposi's sarcoma is a vascular tumor with mixed cellularity that affects individuals with HIV.

• 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.(this is called molecular piracy, which could explain the pathogenesis of the virus , but its pathogenesis is still not clear.)

• 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.

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.

- Knowing that the breast milk is a well documented mode of transmission for this virus and the HTLV-1 virus could help us in preventing infections by counselling mothers.

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

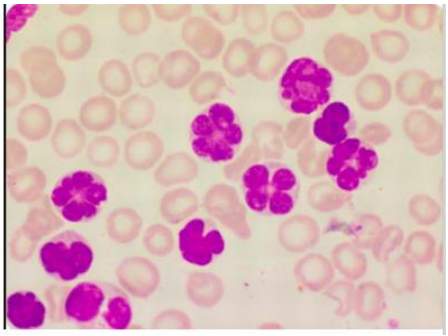
• Foscarnet, famciclovir, ganciclovir, and cidofovir have activity against KSHV replication

HUMAN T-LYMPHOTROPIC VIRUSES

• HTLV-1 has been established as the causative agent of adult T-cell leukemia-lymphomas (ATL) – it is one of the aggressive tumors, a human being can be affected-, the survival rate after 1 year of the diagnosis is less than 5%, as well as a nervous system degenerative disorder similar to multiple sclerosis called tropical spastic paraparesis; HTLV-1-associated myelopathy (HAM) Demyelination of the sheath in the brain and spinal cords, similar to multiple sclerosis.

- The virus is an RNA virus belonging to the same family as HIV, and it is known to be an oncogenic virus. (RETROVIRUS)

• The human lymphotropic viruses have a marked affinity for mature T cells.



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

TRANSMISSION

• Transmission of HTLV-1 seems to involve cell-associated virus, whereas HIV transmission can occur through extracellular means.

• 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 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. It is pathognomonic.

•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.**

الله يا ذا الجلال و العزة ، كن مع اخواننا في غزة

Sheet 3+4