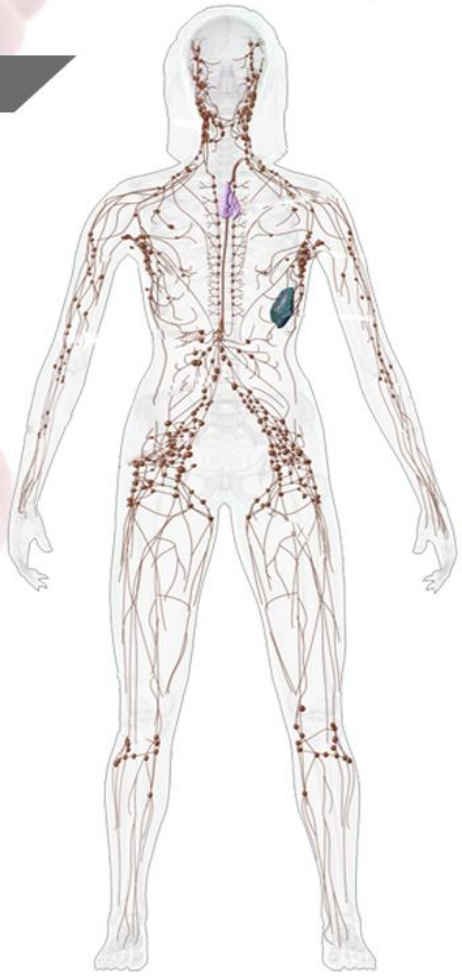
Sheet #

Hematology and Lymphatic system

Subject | Microbiology



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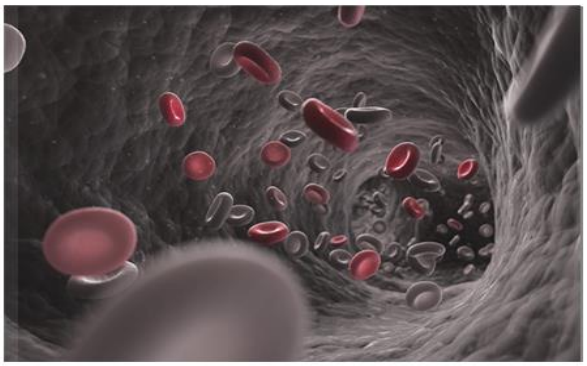

In this lecture we will be interested in many viruses that cause hematopoietic disorders in humans , the focus is going to be on : (B19 parvovirus , HTLV1 , AND, and 2 members of Herpes viruses (EBV andHHV8).

We will start with smallest and simplest one **: Parvovirus**

- This group of viruses have single strand DNA genome of 5000 nucleotides and with single human pathogen type **B19** virus.
- Members Family of parvoviridae, are nonenveloped , icosahedral small (diameter 22 nm) , viruses that contain 5 members , **B 19** is the most common .
- Cell tropism of B19 virus is **erythrocytes** or erythroid progenitor cells.

- Some parvoviruses can only replicate in presence of a helper virus (adeno virus or herpes virus).
- Parvovirus B19 is the only human pathogen identified to date, is capable of autonomic replication , it requires **no** helper virus.
- The outcome of infection is dependent on affected individuals.
- B19 is divided into 3 genotypes 1, 2,3 but only single antigenic type :

Genotype 1 : the most common worldwide.

Genotype 2 : rarely associated with active infection .

Genotype 3 : predominant in western Africa .

Epidemiology:

B19 virus is widespread , infections occur throughout years in all age groups and as outbreaks or as sporadic cases .

Transmission of B19 virus occur mainly through respiratory route , fecal-oral route has been documented as well.

B19 virus target erythroid progenitor cells , this specificity has to do with limited distribution of receptor, the blood group B antigen glycoside, so when infection takes place it leads to viremia and virus will induce a cytotoxic results as incision of RBC production .

However, the outcome is different dependent on the infected individual .

Pathogenesis: Parvovirus B19 replicates in the bone marrow in erythrocyte precursor cells , which are destroyed in the process.

Outcomes of infection of B19 will depend on infected individual immune status:

(4 categories):

- If infection happen in individuals with underlying **hemolysis** disorders ,then there will be transient **aplastic crisis** manifested as severe acute anemia . and in Individuals with normal erythropoiesis , there will be minimal drop in hemoglobin level.

- If affected individual has underlying **immunodeficiency** disorder then will be pure red cell aplasia and these patients will present with **chronic anemia .**

- If infection happen in **pregnant** woman , it appears to cause **spontaneous abortions** in **early** pregnancy and fatal damage in **late pregnancy** (**hydrops fetalis) .**

In otherwise **healthy** persons ,these infections usually run an **asymptomatic** course, however they can also **cause erythema infectiosum** characterized by **cutaneous rash in children** and **Arthralgia arthritis in adults**.

Clinical manifestations :

All infections of B19 are asymptomatic and associated with mild illness.

The **main** manifestation of symptomatic B19 virus infection is : **Erythema infectiosum** which affects **children**, also called **fifth disease or slapped cheek disease.**

Characterized by macular rash on face which give slapped cheek appearance.

In adults, B19 leads to arthralgia which affects small joints of hands , ankles, knees and rest.

Also called **Polyarthropathy syndrome** , uncommon among children ,occurs among 50% of adults , more common among women than men .

Joint pain lasts less than 3 weeks then goes away without any problem .

The second disease associated with B19 virus is (TAC) :

- In most individuals with B19 infection, asymptomatic transient reticulocytopenia occurs, however in patients who depend on continual rapid production of RBCs infection can cause **transient aplastic crisis** .

- Affected individuals include those with **hemolytic** disorders, (hemoglobinopathies , RBCS enzymopathies, autoimmune hemolytic anemia), when become infected with B19 they develop transient aplastic crises .
- If you do bone marrow examination, characteristics of giant pronormoblasts appear .
- Illness is transient, anemia can be resolved.

Third disease associated with B19 virus :**Pure red cell aplasia , chronic anemia**

- This takes place with individuals affected with B19 are **immunodeficient**, including those with congenital immunodeficiency ,AIDS and lymphoproliferative disorders .
- B19 leads to chronic suppression of bone marrow leads to chronic anemia.

- Anemia is severe and patients dependent on blood transfusion .
- Immunodeficient people are either congenital or acquired like those who suffer from AIDs .

Forth disease associated with B19 virus is; **Hydrops fetalis**

- B19 virus is not teratogenic itself.
- Mothers infected with B19 virus may cause serious risk to fetus , a condition know as Hydrops fetalis, in which fetus accumulates fluid , which increase demands of cardiac output leading to heart failure and edema .

Diagnosis of B19 :

- Either we detect virus itself or antigenic part of the virus by means of PCR as well as EM.
- Or we look on specivic response on B19 infection through antibodies IgM and IgG.
- In vitro culturing of the pathogen is not standard procedure.

- In immunocompetent individuals the diagnosis of B19 rely on B19 IgM antibodies .
- B19 Can also be detected at time of rash appearance in erythema infectiosum, usually by third day of transient aplastic crisis.
- B19 IgGs usually detectable by 7^{th} day of illness.

Treatment :

- No antiviral is effective against B19 virus , so treatment often symptomatic .
- Latent infection may acquire transfusion therapy.
- Sometimes , commercial immunoglobulins (IVIG) contain neutralizing antibodies to B19 virus can be given to immunocompromised patients and those with anemia.
- **Intrauterine blood transfusion** can prevent fetal loss in some cases of **hydrops fetalis**.
- There's **no** available vaccine for B19 virus.

Now , we will focus on two members of herpes family: (EPV and HHV8)

- Herpes family includes: (herpes simplex virus HSV (two serotypes) , varicella zoster virus VZV , cytomegalovirus CMV , epstein barr virus EBV , human herpes virus 6 HHV6 and HHV8 .
- All members of herpes have outstanding property, which is ability to establish a lifelong infection on their host and undergo periodic reactivation.

Characteristics of Herpes virus :

- They are double stranded DNA viruses.
- They are enveloped , contain viral glycoprotein.
- Infection with members of Herpes family is a lifelong infection.

Epstein-Barr virus (EPV) :

- It's the cause of heterophile positive infectous mononucleosis (IM) , which characterized by : fever, sore throat , lymph adenopathy and atypical lymphocytosis .
- Cell tropism of EBV is **B lymphocytes**
- EBV is also associated with several tumors including : (nasopharyngeal , gastric carcinoma , Burkitts lymphoma , Hodgkin disease and B cell lymphoma).

- EBV infections occur worldwide, 90% of adults have been seropositive .
- Infection usually biphased, mostly common in early childhood and second peak during late adolescence .

- EPV is excreted in saliva and pharyngeal secretions.
- Main route of EBV transmission is **close contact** and oral secretions so its also called (kissing disease) , however blood transfusion and bone marrow transplantation also reported as modes of transmission .

Pathogenesis ;

- EBV infects narrow spectrum of hosts , they replicate slowly.
- It presents in a latent state of B lymphocytes and can lead to their immortalization as well as tumor transfusion later on.

- EPV enters the body through mucosa , they replicate in epithelial cells of oropharynx , then they enter B lymphocytes when they become in contact with epithelial cells, then they will continue their replication , if lymphocyte proliferation become uncontrollable then this will be first step in a multistep process of neoplastic transformation.

- EBV infects B cells by binding to a viral receptor on B lymphocyte CD21, the same receptor for CD3 of complement system.

- During latent infection of B cells , only (EBV nuclear antigen EBVNA) as well as (latent membrane proteins LMPs) and small EPV RNAs are expressed in vitro .

Clinical manifestations :

- Most infections present in children either asymptomatic or present as mild pharyngitis with or without tonsillitis (thick coating over tonsils)
- In adults , more than 70% of EBV infection present with classic syndrome of infectious mononucleosis, which usually starts 1-2 months occupation period ,then patients start to suffer from severe headache , fever, malaise as well as sore throat , also there might be enlargement of lymph node and spleen , rash might appears on arms and trunk as well.

- Typical illness is self-limited, usually lasts from 2- 6 weeks .

EBV also associated with diseases other than IM , including :

- B cell hyperplasia or poly / mono clonal lymphoma.
- X linked lymphoproliferative disease .
- Oral hairy leukoplakia .
- Burkitts lymphoma .
- Anaplastic nasopharngeal carcinoma.
- Gastric carcinoma.
- Hodkings disease.

The **most** common associated malignancy with EBV is **Gastric carcinoma**.

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

Diagnosis of EBV :

- Patients usually presents with High number of lymphocytes (more than 10% of them are **Atypical**).
- The **most sensitive** mean of detecting EBV is **nucleic acid hybridization** test from patient material (this method is laborious ,time consuming and needs special facilities).

- Serological tests through enzyme linked immunosorbent assays or immunofluorescence,

(individuals with recent infection usually have IgM, IgG antibody and viral capsid antigen).

- Monospot test in which transient netrophilic antibodies can develop and agglutinate. (its rapid and confirmatory test

Treatment :

Acyclovir reduces EBV shedding from the oropharynx during the period of drug administration , but it **doesn't** 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 immune compromised patients .

There is no EBV vaccine available .

Human Herpes virus 8 (kaposi sarcoma Herpes Virus)

- Also called kaposi sarcoma

(KSHV) It is the cause of KS ,vascular tumors of mixed cellular composition in AIDs patients .

- Kaposi sarcoma genome contain numerous cells , regulatory genes that contribute to its pathogenesis .

Transmission :

Close contact with infected oral secretions, Sexually as well as vertically from mother to baby, it also can be transmitted through blood transfusion and organ transplantation.

Diagnosis:

- Either by identification of virus itself or antigenic parts of virus by PCR.
- Direct virus culture is difficult and impractical.
- Indirectly, through immunofluorescence, western blot or ELISA .

Treatment:

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

Human T-lymphocytic virus :

- As the name indicates target of this virus is T-**lymphocytes** .
- They are retrovirus , RNA viruses.
  Retrovirus two subfamliliy :

1- Delta virus which contain (HTLV1)
2- *Lentivirus* which contain(HIV)

- HTLV is the main causative agent of **adult T Cell leukemia lymphomas** (ATL) , as well as a nervous system degenerative disorder called tropical spastic paralysis (HTLV1- associated myelopathy HAM)
- Latency period usually between 20-30 years before onset of leukemia.

- **Transmission** : at least through 3 routes :
- Mother to baby (breast milk)
- Sexual activity
- Through blood transfusion or contaminated needle .

Clinically :

- HTLV1 infection is usually asymptomatic but can progress to can progress to ATLL in approximately 1 in 20 persons over a 30 years old .
- ATLL caused by HTLV1 is a neoplastic of the CD4 helper T cells can be acute or chronic.
- Under microscope , CD4 cells appear as flower cells because of multi lobulated nuclei .

Diagnosis :

- Serology ELISA , western blot .
- Viral PCR.

Treatment : no specific antiviral therapy , however **combination** of **interferon alpha** and **zidovudine** may extend survival.

- no particular treatment approved to ATLL

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 prevention of HIV infection, the practice of safe sex and the avoidance of needle sharing are important .

Best of luck