MICROBIOLOGY

بسم الله الرحمن الرحيم

MID – Lecture 4

Herpesviruses (Pt.2)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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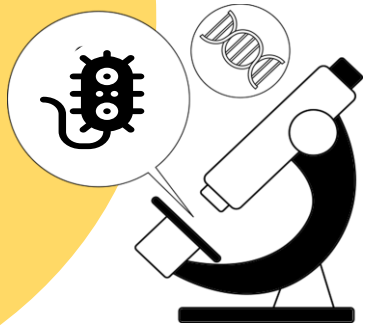
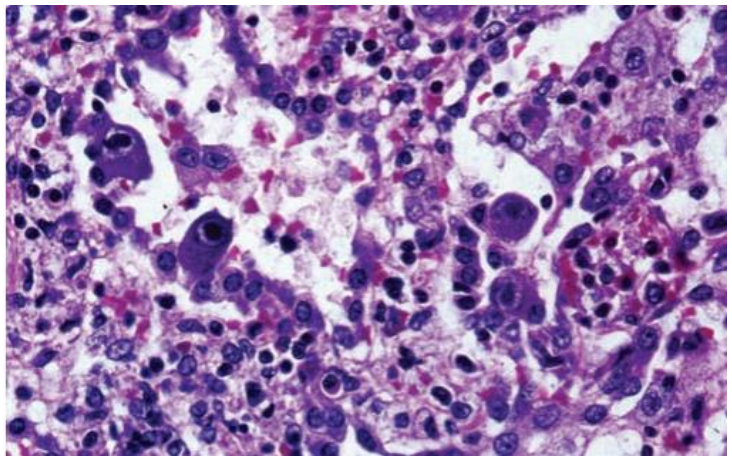


3- Cytomegalovirus (CMV)

- The virus is named Cytomegalovirus due to its cytopathic effects, including cell enlargement (cytomegaly) and the presence of inclusion bodies in multinucleated cells, giving it a cytomegalic appearance.
- This virus shares structural, replication, and latency characteristics with other herpesviruses. Its genome is larger compared to others, and unlike them, it does not cause a skin rash. Instead, it invades internal organs and tissues, where it persists and induces cytopathic effects. Its impact on the skin is limited.

Recall: Herpes simplex causes mouth or genital ulcers.
Varicella-zoster causes chickenpox and shingles.

owl's eye



Epidemiology

- Neonatal and perinatal transmissions are considered vertical.
- postnatal transmission is considered horizontal.

- CMV is one of the most successful human pathogens, it can be transmitted vertically or horizontally **usually** with little effect on the host (subclinical appearance).
- Once infected, the person carries the virus for life **(latency)** which may be activated from time to time, especially in immunocompromised individuals, during which infectious virions **(shedding)** appear in the urine and the saliva.
- The virus may be transmitted in utero, perinatally, or postnatally.
  - Perinatal infection is acquired mainly through infected genital secretions or breast milk. Overall, 2-10% of infants are infected by the age of 6 months worldwide.
  - Postnatal infection mainly occurs through saliva. Sexual transmission may occur as well as through blood and blood products and transplanted organ.
- In developed countries with a high standard of hygiene, 40% of adolescents are infected and ultimately 70% of the population is infected. In developing countries, over 90% of people are ultimately infected.

Clinical Manifestations

- Congenital, perinatal, and postnatal infections are classified as primary infections.
- Reactivation or reinfection is considered a secondary infection.

- Congenital infection - may result in cytomegalic inclusion disease.

Defined as the isolation of CMV from the saliva or urine within 3 weeks of birth. The second most common cause of mental handicap (mental retardation) after Down's syndrome and is responsible for more cases of congenital damage than rubella

- Perinatal infection (up to 6 months) - usually asymptomatic
- Postnatal infection (adulthood)- usually asymptomatic. However, in a minority of cases, the syndrome of **infectious mononucleosis** may develop which consists of fever, lymphadenopathy, and splenomegaly. Atypical lymphocytes may be found in the blood.
    - This disease shares symptoms with **Epstein-Barr virus**, causing fever, splenomegaly, lymphadenopathy, and lymphocytosis. It primarily targets B lymphocytes and often presents with clinical manifestations similar to infectious mononucleosis, affecting the immune system in a comparable way.
- Immunocompromised patients are prone to **severe** CMV disease such as pneumonitis, retinitis, colitis, and encephalopathy.
- Reactivation or reinfection with CMV is usually asymptomatic **except** in immunocompromised patients.

Laboratory Diagnosis

- make an accurate diagnosis, it is essential to understand the virus, the history of contact, the primary infection, and its shedding in urine and saliva.
  - Direct detection
    - Biopsy specimens may be examined histologically for CMV inclusion antibodies or for the presence of CMV antigens.
    - The **pp65** CMV antigenaemia test is used for the rapid diagnosis of CMV.
  - Virus Isolation
    - Conventional cell culture requires up to **4 weeks for results.**
    - More useful are rapid culture methods such as the DEAFF test which can provide a result in 24-48 hours.

      The best cellular culture for CMV is **human fibroblast cells.**
  - Serology
    - The detection of IgM is indicative of primary infection.
    - The presence of CMV IgG antibody indicates past infection.
  - PCR for CMV-DNA

CMV pp65 antigenaemia test

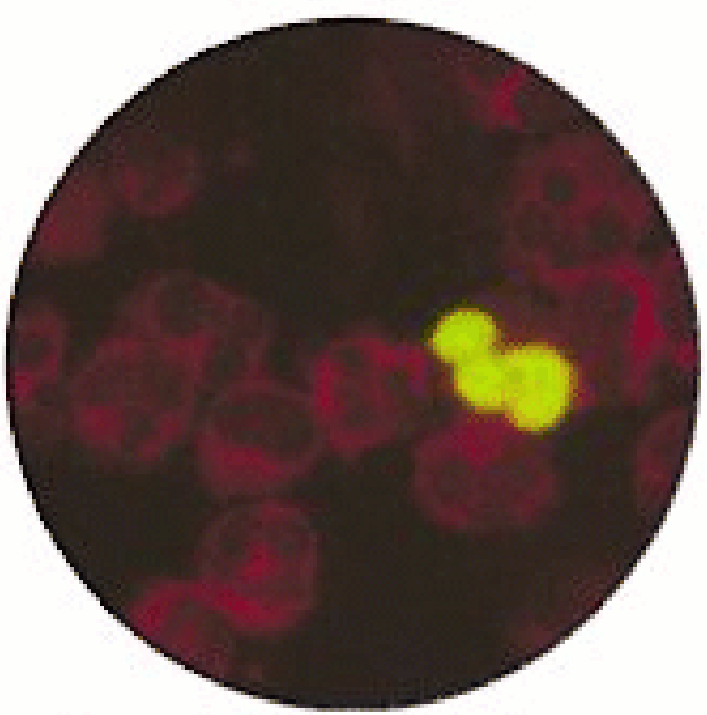


Figure 4 CMV pp65 antigens detected in nuclei of peripheral blood neutrophils

DEAFF test for CMV

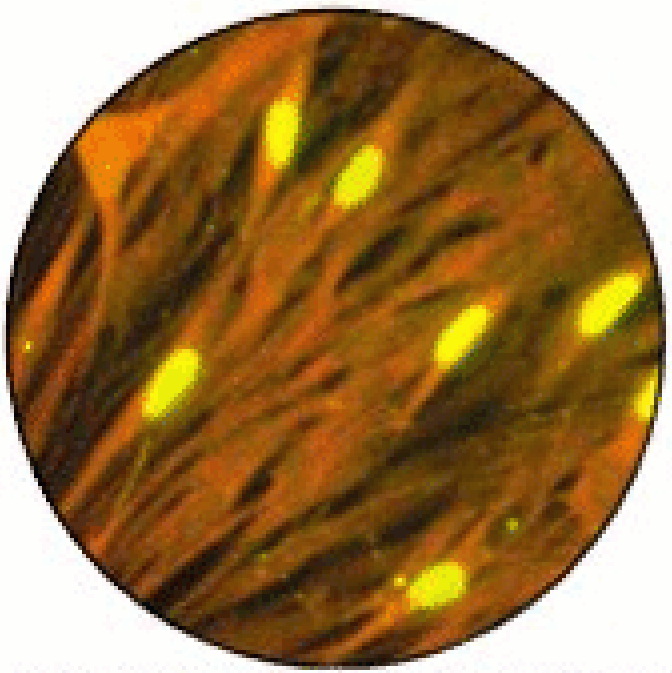


Fig. 2, CMV centrifugation culture fixed and stained 16 hrs after inoculation showing viral proteins in nuclei of infected human fibroblast cells

Treatment

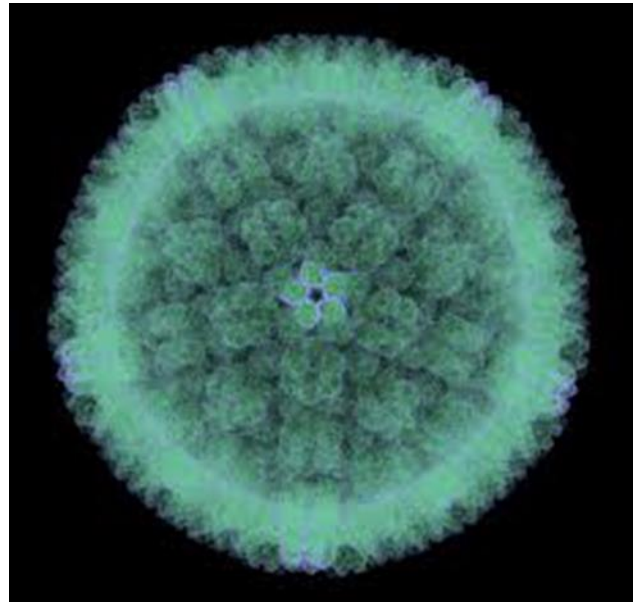
- Congenital infections - it is not usually possible to detect congenital infection unless the mother has symptoms of primary infection. If so, then the mother should be told of the chances of her baby having cytomegalic inclusion disease and perhaps offered the choice of an abortion.
- Perinatal and postnatal infection - it is usually not necessary to treat such patients.
- Immunocompromised patients - it is necessary to make a diagnosis of CMV infection early and give prompt antiviral therapy **(ganciclovir).**
- No licensed vaccine is available.

Clarification Regarding the previous slide

- Congenital infection. (Cases)
  - In the first state, neither the mother nor the fetus show symptoms, and the infection can only be detected through a positive virus test.
  - In the second state, the mother shows symptoms, or the fetus has an enlarged head and abnormal brain development, which can be detected through ultrasound.
  - Some countries have implemented screening programs for this virus, especially for mothers.

4- Epstein-Barr Virus (EBV)

- Follows the main characteristics of herpesvirus (structure, replication and pathogenesis).
- Their target cells, however, are neither skin nor visceral cells; They are B lymphocytes.



Epidemiology

- Two epidemiological patterns are seen with EBV

1. In developed countries, 2 peaks of infection are seen : the **first** in very young preschool children aged 1 - 6 and the **second** in adolescents and young adults aged 14 – 20. Eventually 80-90% of adults are infected.

   You probably contracted the virus without even knowing, **as most cases are asymptomatic.**

2. In developing countries, infection occurs at a much earlier age so that by the age of two, 90% of children are seropositive.

- The virus is transmitted by contact with saliva, particularly through kissing. As most herpesvirus

Pathogenesis and diseases

- Once infected, a lifelong carrier state develops whereby a low-grade infection is kept in check by the immune defenses.
- Low-grade virus replication and shedding can be demonstrated in the epithelial cells of the pharynx of all seropositive individuals. (Primary infection)
- EBV can immortalize B-lymphocytes in vitro and in vivo
- Disease Associations:

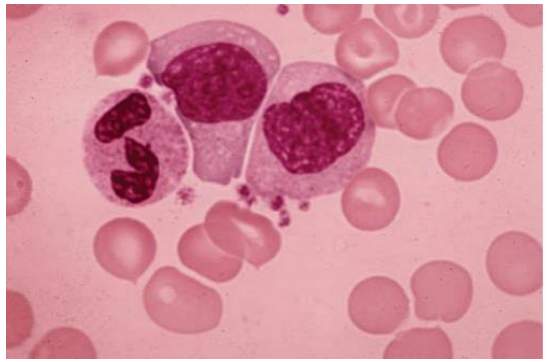
1. Infectious Mononucleosis — A syndrome associated with many herpesvirus (common, benign and self limited). As in CMV, which is called infectious mononucleosis like disease.
2. Burkitt's lymphoma — Lymph node cancer
3. Nasopharyngeal carcinoma — Pharynx cancer
4. Lymphoproliferative disease and lymphoma in the immunosuppressed.

Clarification Regarding the previous slide

- Complete recovery is impossible, the virus will still be present as a **latent** infection.
- A person infected by this virus will be a lifelong **carrier**.
- The virus is usually dealt with by the immune system, and in rare cases replication and shedding might occur.
  1. The primary infection site is the **pharynx**, and the saliva turns positive.
  2. Then the virus moves to the **B lymphocytes** (target cells). The virus may change the shape of the B cells. Shedding is usually positive.
- Shedding **intermittently** occurs, especially during states of immunodeficiency.
- The virus can cause the B lymphocytes to undergo 2 changes either in vitro or in vivo:
  1. Become **immortal**.
  2. **A change in shape** is common and it's called atypical lymphocytosis (cytopathic effect)

Infectious Mononuclosis

Most common presentation in adults.



- Primary EBV infection is usually subclinical in childhood. However, in adolescents and adults, there is a 50% chance that the syndrome of infectious mononucleosis (IM) will develop.
- IM is usually a self-limited disease which consists of fever, lymphadenopathy, and splenomegaly. Atypical lymphocytes are present in the blood.
- Complications occur rarely but may be serious e.g. splenic rupture, meningoencephalitis, and pharyngeal obstruction.
- Diagnosis of IM is usually made by detection of EBV IgM.
- There is no specific treatment.

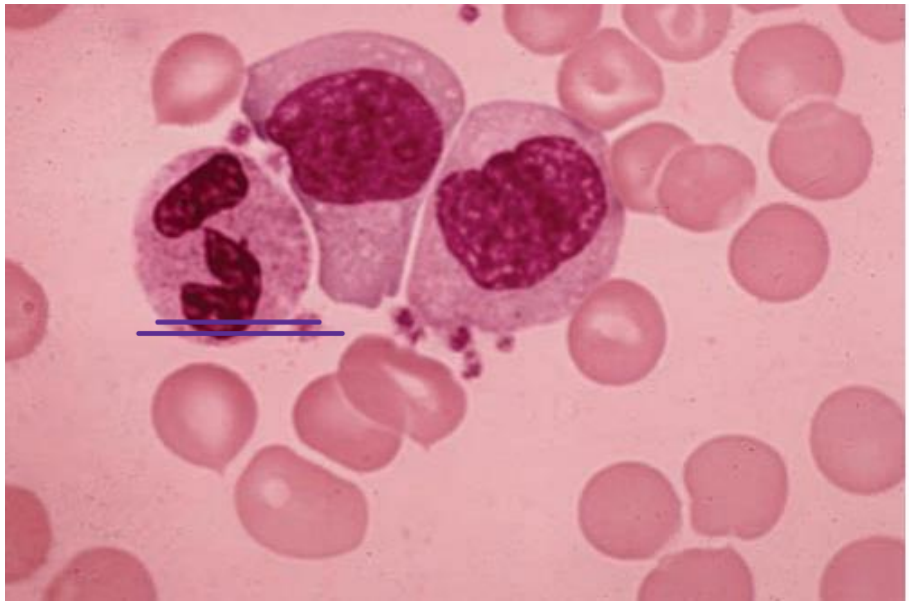
Clarification Regarding Infectious Mononucleosis 1

- The virus targets **lymphoid** organs like the **lymph nodes** causing lymphadenopathy and the **spleen** causing splenomegaly.
- Recall that the virus causes immortalization of B lymphocytes, this in turn causes atypical lymphocytes (high count and different shape) Normal B lymphocytes contain A single circular large nucleus and a Small cytoplasm

Clarification Regarding Infectious Mononucleosis 2

- Complications are usually serious.
- Infected patients are susceptible to **splenic rupture**, which is a serious surgical matter. The spleen can't be repaired so the only solution is a splenectomy.
- **Meningoencephalitis** may also occur.
- The virus might cause enlargement and an edema in the pharynx leading to **pharyngeal obstruction .**

- This is an abnormal B-lymphocyte, multinucleated and enlarged.
- Note that this is a blood film, which is a crucial component in diagnosing infectious mononucleosis.



Burkitt’s Lymphoma

cancer in lymph nodes and B lymphocytes. Lymphadenopathy with tumor cells

- Burkitt's lymphoma (BL) occurs endemically in parts of **Africa** (where it is the commonest childhood tumour).
- It usually occurs in children aged 3-14 years. It responds **favorably to chemotherapy.**
- It is restricted to areas with endemic malaria. Therefore, **it appears that malaria infection is a cofactor.**
- Burkitt’s lymphoma should be diagnosed by **histology**. The tumour can be stained with antibodies to lambda light chains showing a monoclonal tumour of B-cell origin. We prepare a histological section from affected lymph node, bone marrow, or peripheral blood and examine it to identify tumor B-lymphocytes which have special antibody for lambda light chain.
- In theory BL can be controlled by vaccination against EBV.
- This vaccine is being tried in Africa.
- The diagnosis of infectious mononucleosis is based on symptoms, blood lymphocytosis, and positive IgM, whereas the diagnosis of Burkitt lymphoma follows a different approach.

Nasopharyngeal Carcinoma

- Nasopharyngeal carcinoma (NPC) is a malignant tumour of the **squamous epithelium** of the nasopharynx. It is very prevalent in South China, where it is the commonest tumour in men and the second commonest in women.
- The tumour is rare in most parts of the world. **(It is due to the environmental factors in that area).**
- Besides EBV, there appear to be several environmental and genetic cofactors in NPC.
- Cases of NPC should be diagnosed by **histology**.
- NPC usually presents late and thus the prognosis is poor.
- In theory NPC can be prevented by vaccination against EBV.

5- Human Herpes Virus 6, 7, 8

They follow in general characteristics herps virus (structure, latency, replication ....),
but unfortunately there isn't much information about those viruses, we know few details about diseases it can cause and about any other clinical manifestation.

Epidemiology and Pathogenesis

- HHV-6 and HHV-7 are found worldwide.
- They are transmitted mainly through contact with saliva and through breast feeding.
- HHV-6 and HHV-7 infection are acquired rapidly after the age of 4 months when the effect of maternal antibody wears off. This occurs usually after 4 months to 6 months maximum.
- By the time of adulthood, 90-99% of the population had been infected by both viruses.

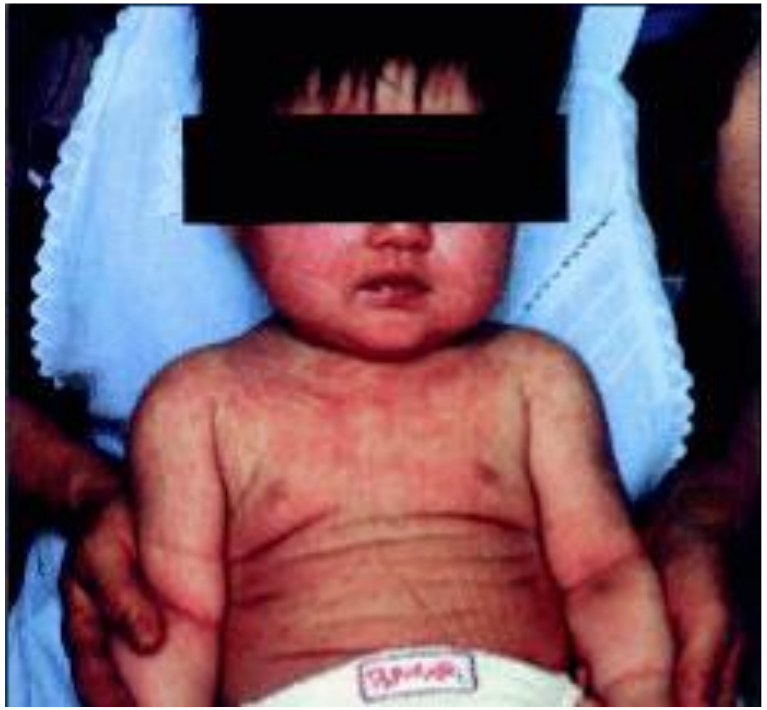
  Luckily most of them are either asymptomatic or mild infections.
- Like other herpesviruses, HHV-6 and HHV-7 remains latent in the body after primary infection and reactivates from time to time. Especially in immunocompromised people.
- The main target cell is the **T-lymphocyte (mainly)**, although B-lymphocytes may also be infected.

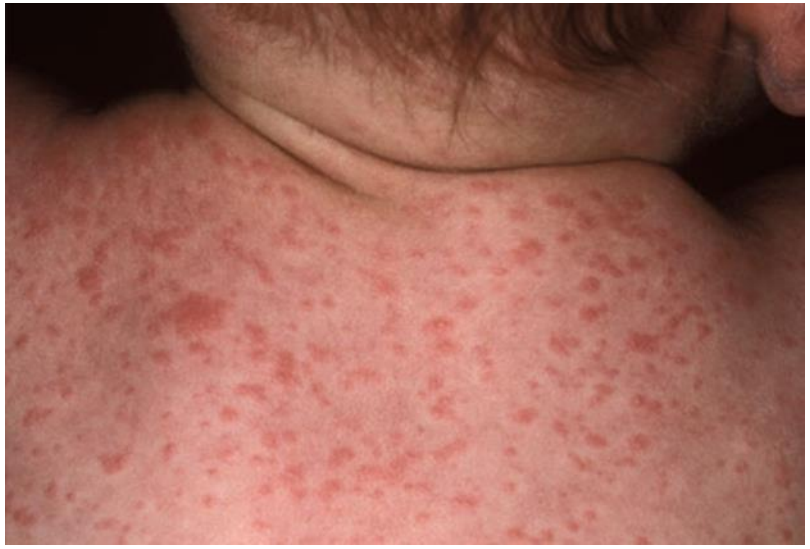
Clinical Manifestations

- Primary HHV-6 infection is associated with Roseala Infantum
- Most cases occur in infants between the ages of 4 months and two years.
- A spiking fever develops over a period of 2 days followed by a mild rash. Usually benign and self limited.
- If primary infection is delayed until adulthood, there is a small chance that an **infectious mononucleosis-like disease** may develop similar to **EBV** and **CMV**.
- There is no firm evidence linking HHV-6 to lymphomas or lymphoproliferative diseases.
- There is no firm disease association with HHV-7 at present.
- Although both viruses may be reactivated in immunocompromised patients, it is yet uncertain whether they cause significant disease.
- HHV-8 is firmly associated with **Kaposi's sarcoma** (Kaposi's sarcoma-associated herpesvirus), DNA is found in almost 100% of cases of Kaposi's sarcoma.

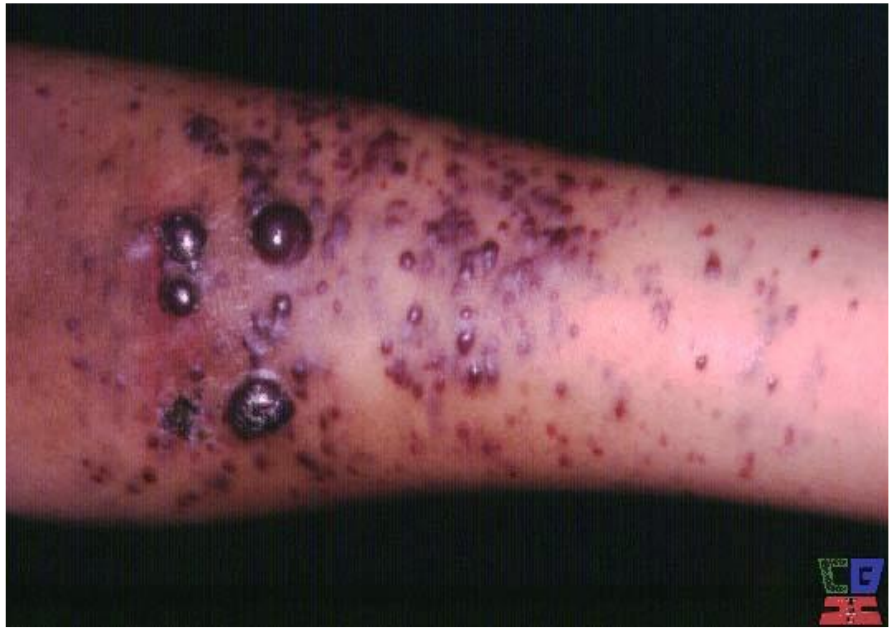
Type of cancer, appear as black spots in the skin.
Common in immunocompromised people (like HIV), and it might be the death cause in latent stage.

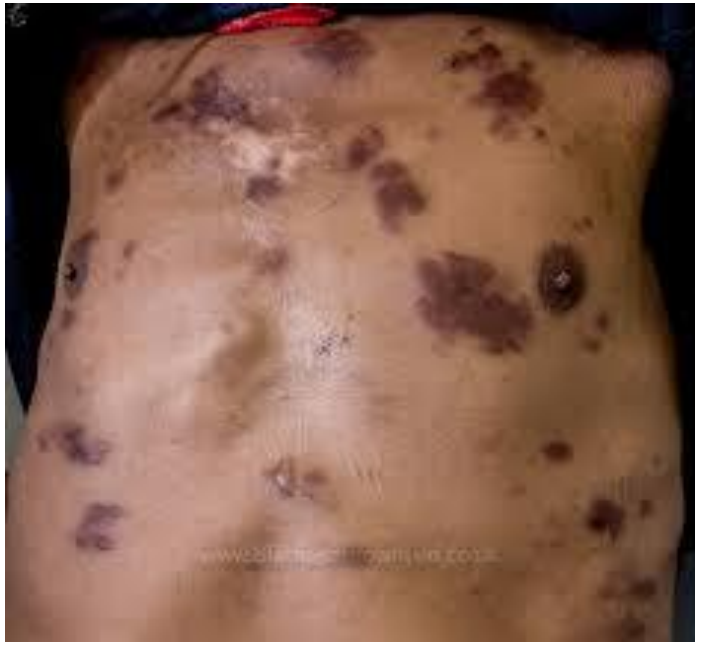
HHV-6 Roseala Infantum





HHV-8 Kaposi's Sarcoma





Very distinctive and special to Kaposi's Sacroma.

Diagnosis and Management

- Rosela Infantum has a very characteristic presentation and a diagnosis can usually be made on clinical grounds alone.
- The technique for virus isolation is complicated and thus not practicable as a routine diagnostic procedure.
- Serology is the mainstay of diagnosis where specific IgM and IgG are detected.
- There is no specific antiviral treatment for HHV-6 infection.

Summary		
Virus	**Main Conceptual Context**	**Key Characteristics and Associated Clinical Details**
Cytomegalovirus (CMV)	Characterized by cytopathic effects such as cell enlargement and inclusion bodies. Does not cause skin rash; invades internal organs.	Associated with congenital infections (mental retardation, cytomegalic inclusion disease). Can reactivate, causing severe diseases in immunocompromised individuals.
Epstein-Barr Virus (EBV)	Targets B lymphocytes, causes infectious mononucleosis and cancers (Burkitt's lymphoma, Nasopharyngeal carcinoma).	Primary infection often subclinical; in adults, it can cause infectious mononucleosis (fever, lymphadenopathy). May lead to immortalization of B lymphocytes.
Human Herpes Virus 6 (HHV-6)	Primarily affects T-lymphocytes; associated with Roseola Infantum in children.	Causes spiking fever followed by mild rash. May cause mononucleosis-like symptoms if infection is delayed to adulthood.
Human Herpes Virus 7 (HHV-7)	Similar to HHV-6 in characteristics but no firm disease association established.	Mostly asymptomatic or mild infections. Reactivates occasionally, especially in immunocompromised individuals.
Human Herpes Virus 8 (HHV-8)	Associated with Kaposi's sarcoma, particularly in immunocompromised individuals.	Presents as dark skin lesions. Commonly affects patients with HIV.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			