7- Herpesviruses

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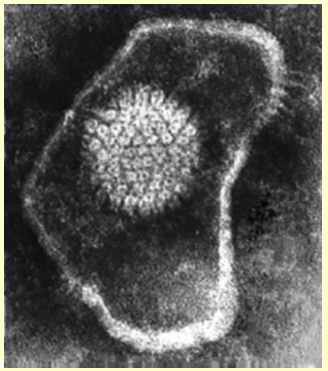
Objectives

- Discuss the morphology, epidemiology, pathogenesis, clinical presentation, laboratory diagnosis and management of:

1. Herpes Simplex virus Type 1 (HSV-1)
2. Herpes Simplex virus Type 2 (HSV-2)
3. Epstein Barr virus (EBV)
4. Cytomegalovirus (CMV)
5. Varicella Zoster virus (VZV)
6. Human Herpes virus 6 (HHV-6)
7. Human Herpes virus 8 (HHV-8)

Introduction



- Herpes Viruses are a leading cause of human viral diseases, second only to influenza and cold viruses
- The outstanding property of herpesviruses is their ability to establish lifelong persistent infections in their hosts and to undergo periodic reactivation
- Reactivation is more likely to take place during periods of immunosuppression and in the elderly
- All herpesviruses have identical morphology and cannot be distinguished from each other under electron microscopy.

Classification

Group	Biological characteristics	Members
Alpha herpesviruses	fast-growing, cytolytic, establish latent infections in neurons	HSV-1, HSV-2, VZV
Beta herpesviruses	slow growing, cytomegalic, become latent in secretory glands and kidneys	CMV, HHV-6, HHV-7
Gamma herpesviruses	Variable, lymphoproliferative, e latent in lymphoid cells	EBV, HHV-8

General properties

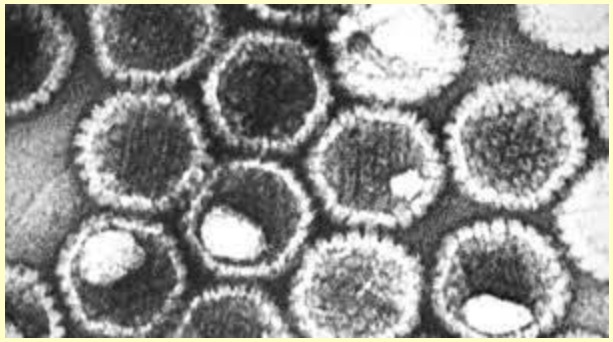


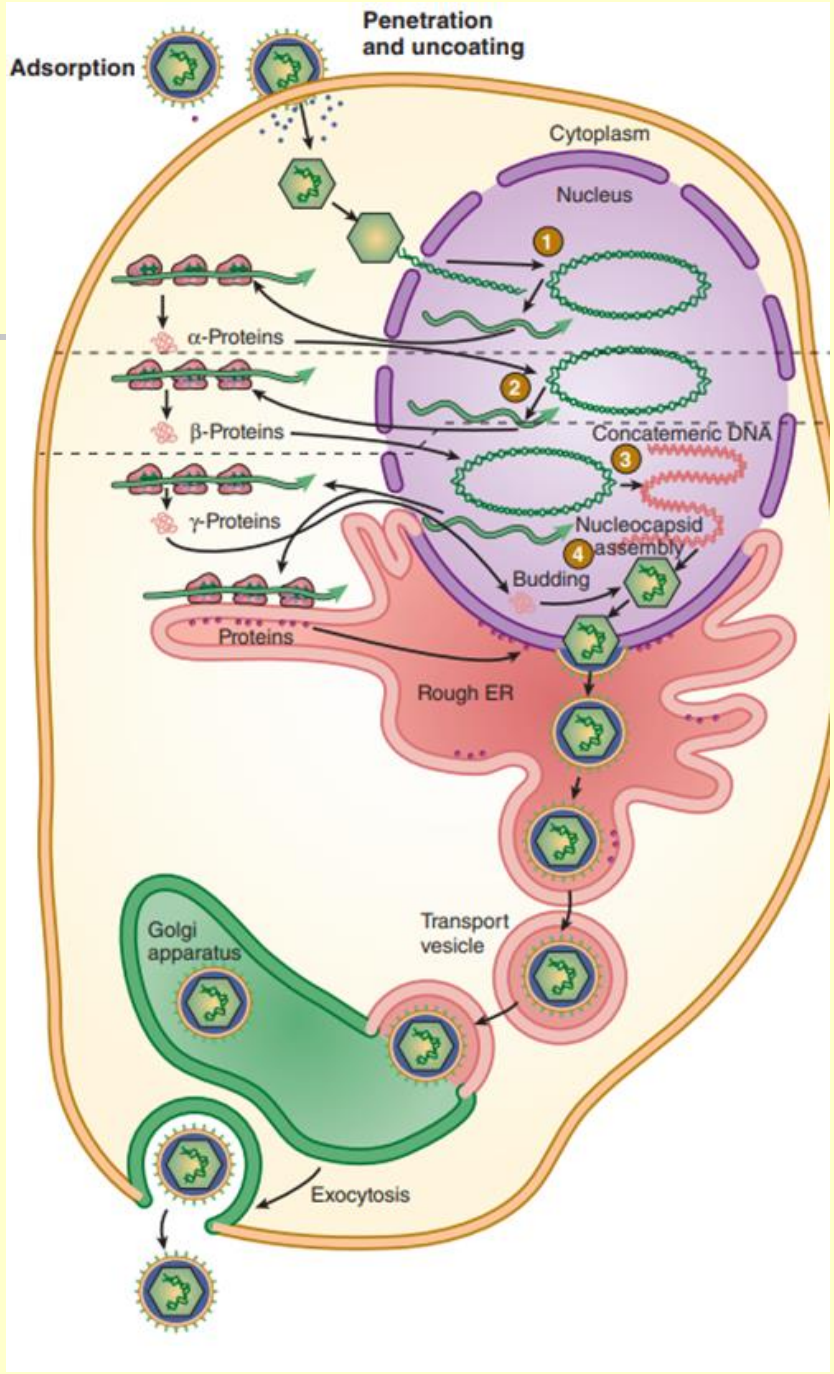
TABLE 33-1 Important Properties of Herpesviruses

Virion: Spherical, 150–200 nm in diameter (icosahedral)
Genome: Double-stranded DNA, linear, 125–240 kbp, reiterated sequences
Proteins: More than 35 proteins in virion
Envelope: Contains viral glycoproteins, Fc receptors
Replication: Nucleus, bud from nuclear membrane
Outstanding characteristics:
Encode many enzymes
Establish latent infections
Persist indefinitely in infected hosts
Frequently reactivated in immunosuppressed hosts
Some cause cancer

Replication

1. α-Proteins, products of immediate-early genes, stimulate transcription of early genes.
2. β-Proteins, products of early genes, function in DNA replication, yielding concatemeric DNA.
3. γ-Proteins, products of late genes and consisting primarily of viral structural proteins, participate in virion assembly

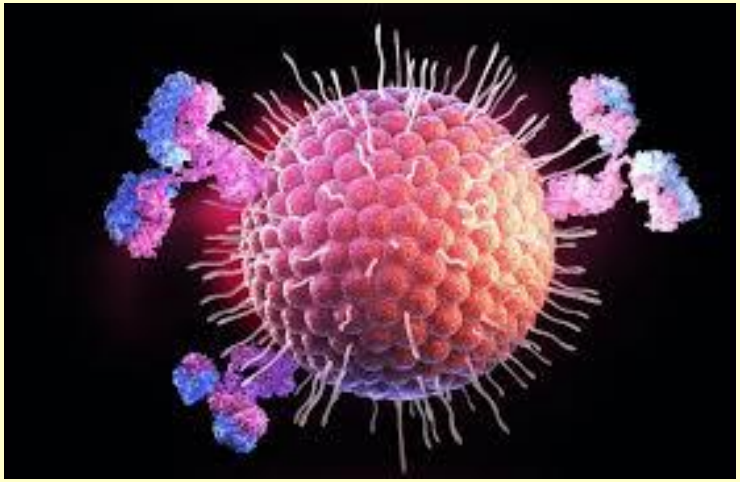
They encode a large number of enzymes/proteins (70-200)



Important clinical viruses

- There are 25 families in the Herpeotoviridae but only 7 of them infect man:
  - Herpes Simplex virus Type 1 (HSV-1)
  - Herpes Simplex virus Type 2 (HSV-2)
  - Epstein Barr virus (EBV)
  - Cytomegalovirus (CMV)
  - Varicella Zoster virus (VZV)
  - Human Herpes virus 6 (HHV-6)
  - Human Herpes virus 8 (HHV-8)

1- Herpes Simplex Viruses (HSV)



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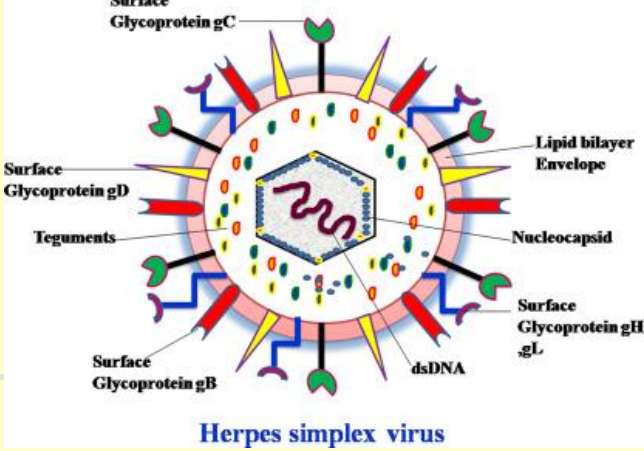


Herpes simplex virus

- Belong to the alpha herpesvirus subfamily of herpesviruses
- HSV-1 and HSV-2 infect epithelial cells and establish latent infections in neurons
- Type 1 is associated with oropharyngeal lesions (above the belt) while Type 2 infects the genital mucosa (below the belt), though the anatomical specificity of these viruses is diminishing
- Classically, HSV-1 is spread by contact with infected saliva and HSV-2 is transmitted sexually
- The genome of HSV-1 and HSV-2 share 50 - 70% homology.
- They also share several cross-reactive epitopes with each other.

Epidemiology

- HSV is spread by contact, as the virus is shed in saliva, tears, genital and other secretions.
- By far the most common form of infection results from a kiss given to a child or adult from a person shedding the virus.
- There are 2 peaks of incidence, the first at 0 - 5 years and the second in the late teens when sexual activity commences.
- About 10% of the population acquires HSV infection through the genital route and the risk is concentrated in young adulthood.
- Following primary infection, 45% of orally infected individuals and 60% of patients with genital herpes will experience recurrences.

Pathogenesis and Pathology

- Because HSV causes cytolytic infections, pathologic changes are due to necrosis of infected cells and inflammation
- During the primary infection, HSV spreads locally and a short-lived viraemia occurs. Spread to the craniospinal ganglia (trigeminal or sacral ganglia) through retrograde axonal flow and establishes latency.
- Virus resides in latently infected ganglia in a nonreplicating state and persists for life
- Reactivation/recurrence is triggered by physical or psychological stress, infection, fever, or ultraviolet and sunlight
- The virus transits via axons back to the peripheral site, and replication proceeds at the skin or mucous membranes

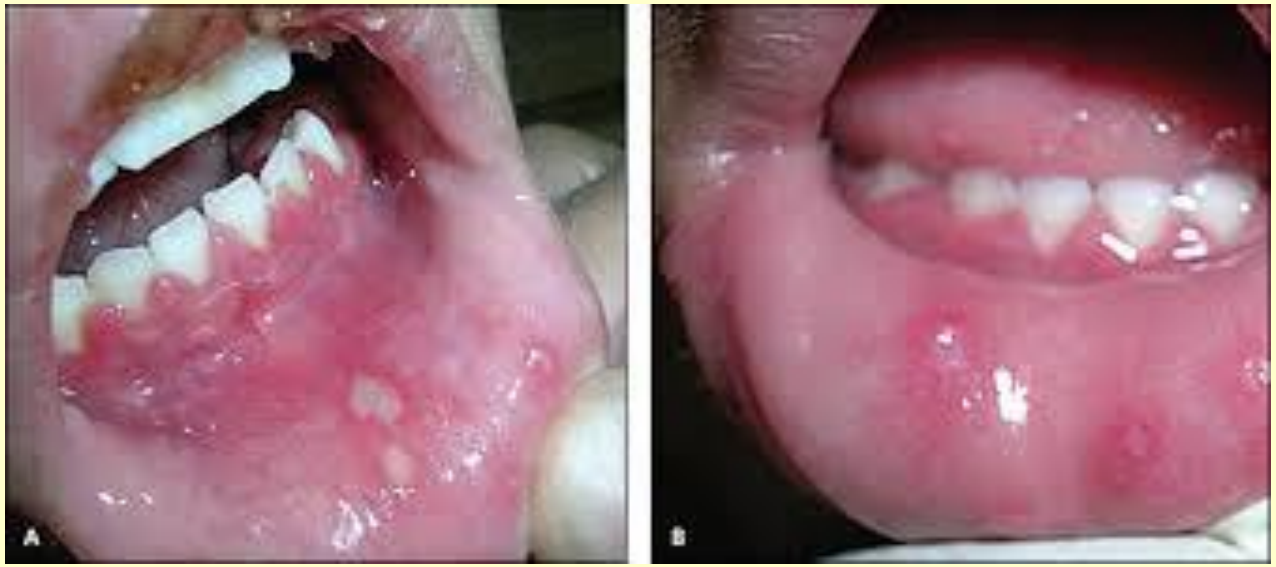
Clinical Manifestations

HSV is involved in a variety of clinical manifestations which includes;-

1. Acute gingivostomatitis
2. Herpes Labialis (cold sore)
3. Ocular Herpes
4. Herpes Genitalis
5. Meningitis/Encephalitis
6. Neonatal herpes

Oral-facial Herpes (HSV-1)

- **Acute Gingivostomatitis**
  - The commonest manifestation of primary herpetic infection.
  - The patient experiences pain and bleeding of the gums. 1 - 8 mm ulcers with necrotic bases are present. Neck glands are commonly enlarged accompanied by fever.
  - Usually a self-limiting disease that lasts around 13 days.
- **Herpes labialis (cold sore)**
  - Following primary infection, 45% of orally infected individuals will experience reactivation.
  - Herpes labialis (cold sore) is a recurrence of oral HSV.
  - A prodrome of tingling, warmth, or itching at the site usually heralds the recurrence. About 12 hours later, redness appears followed by papules and then vesicles.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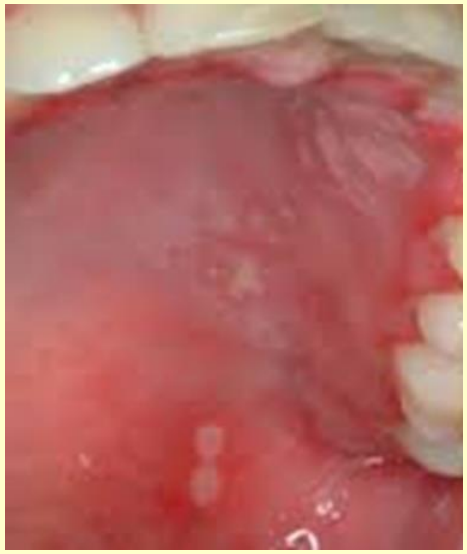
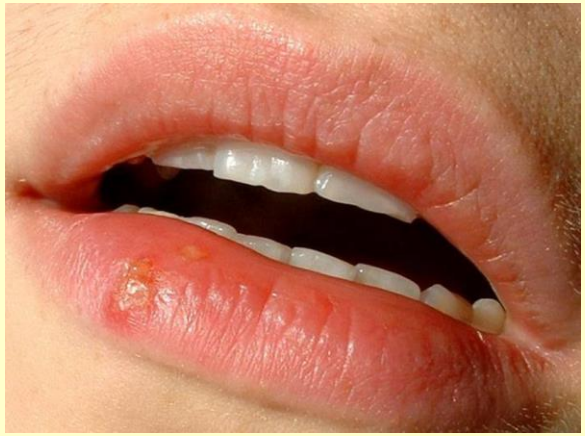
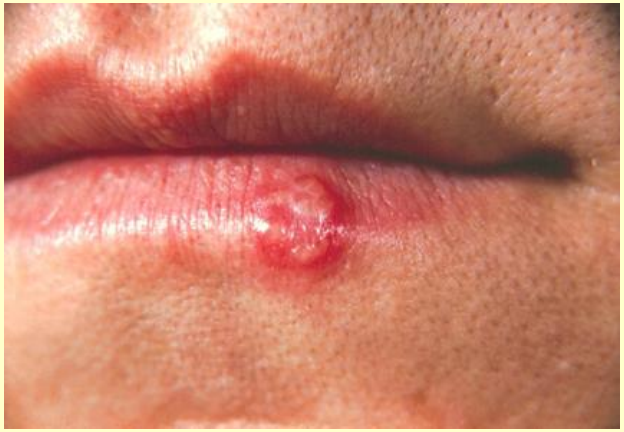
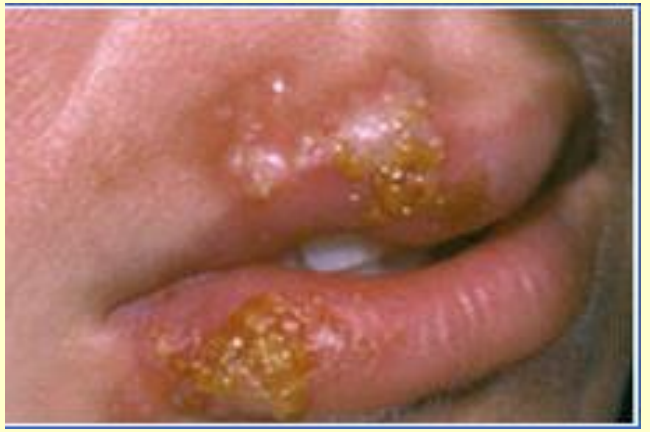






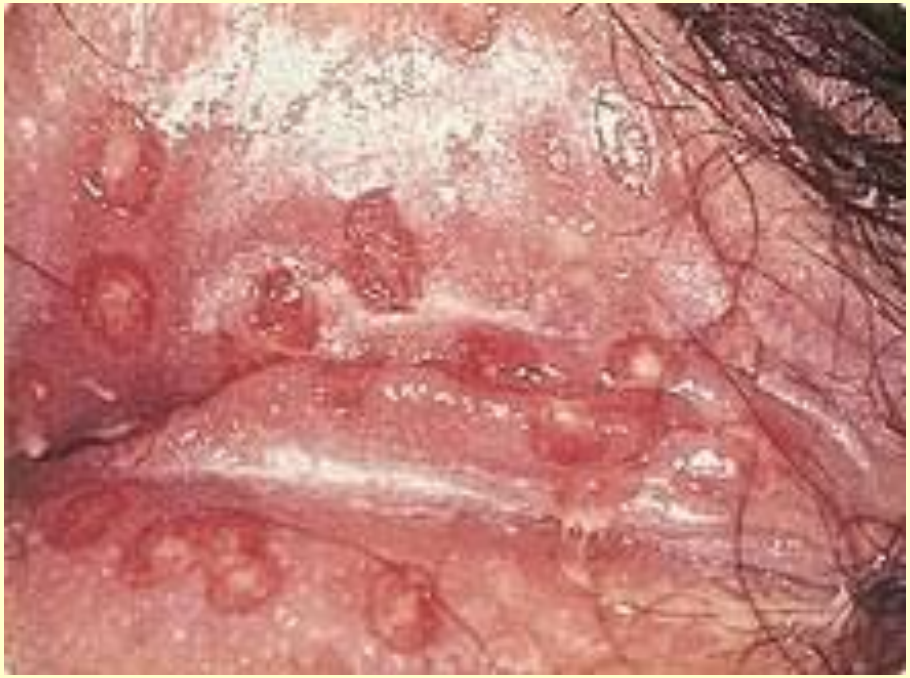


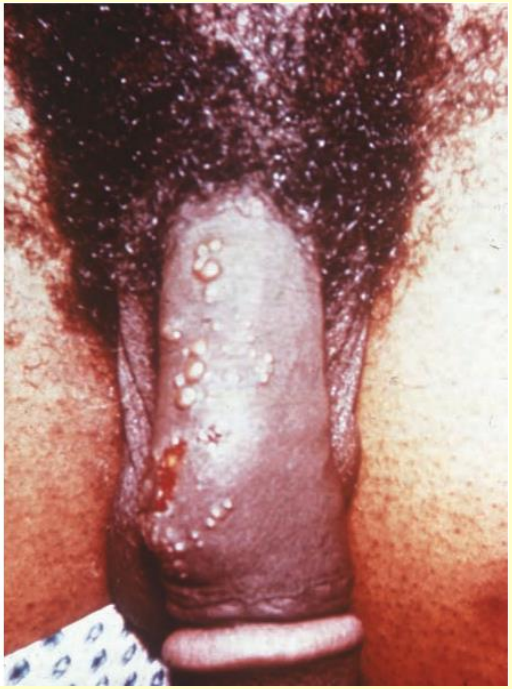
Ocular herpes

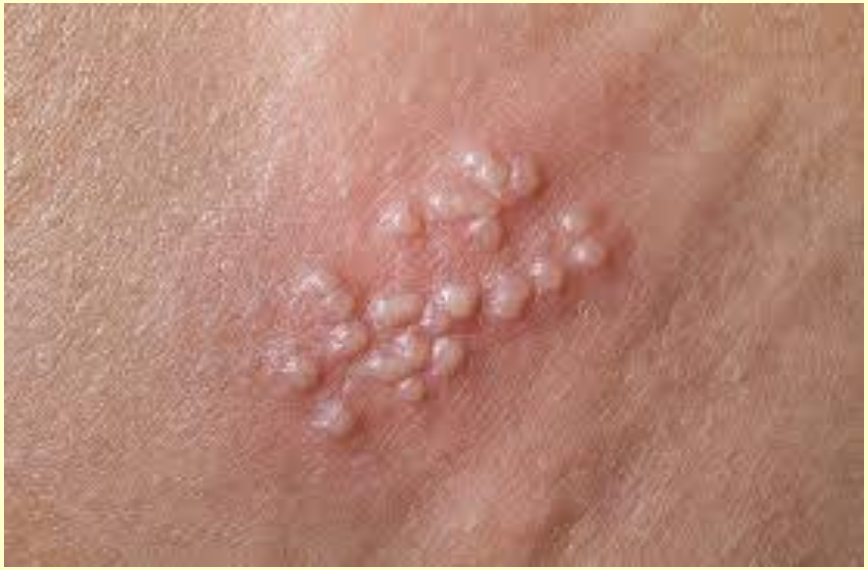
- HSV infections may occur in the eye, producing severe keratoconjunctivitis
- Recurrent lesions of the eye are common and appear as dendritic keratitis or corneal ulcers or as vesicles on the eyelids
- With recurrent keratitis permanent opacification and blindness might occur

Genital Herpes (HSV-2)

- Genital herpes is characterized by vesiculoulcerative lesions of the penis of the male or of the cervix, vulva, vagina, and perineum of the female
- lesions are very painful and may be associated with fever, malaise, dysuria, and inguinal lymphadenopathy.
- The lesions of genital herpes are particularly prone to secondary bacterial infection
- 60% of patients with genital herpes will experience recurrences.
- Recurrent lesions in the perianal area tend to be more numerous and persists longer.







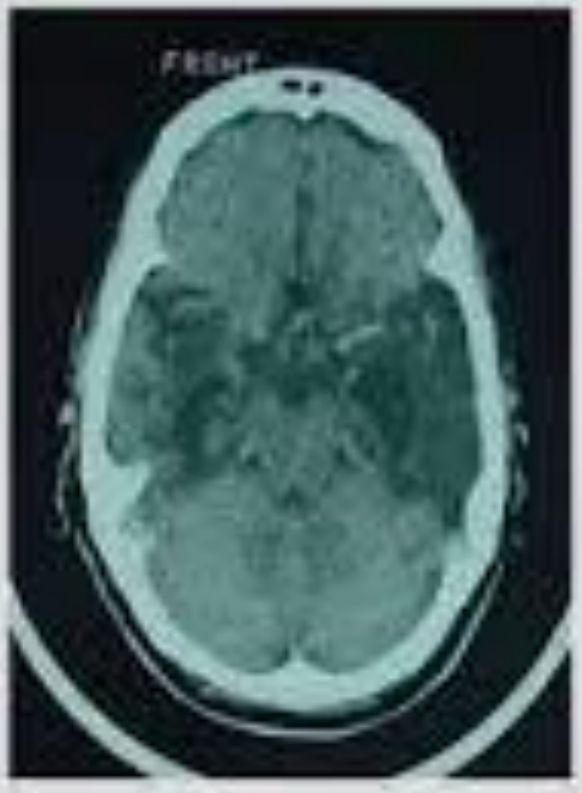
Herpes Simplex Encephalitis

- Herpes Simplex meningitis or encephalitis is one of the most serious complications of herpes simplex disease. There are two forms:

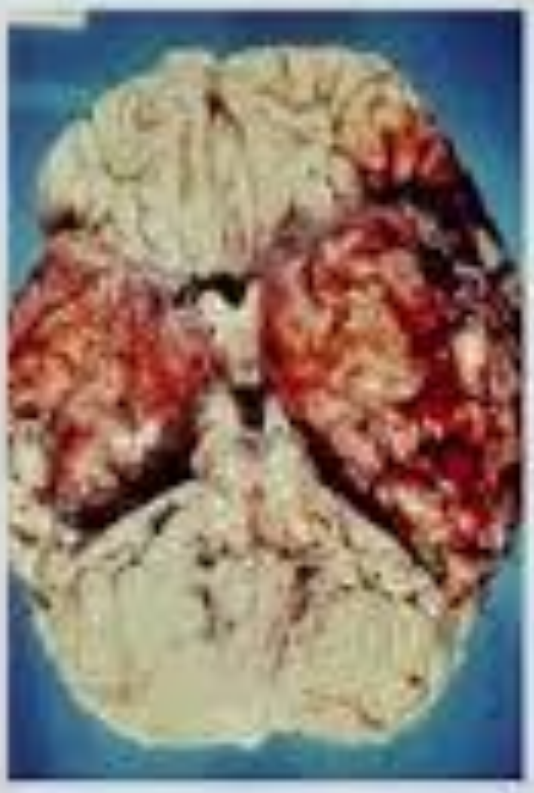
1. Neonatal – there is global involvement and the brain is almost liquefied. The mortality rate approaches 100%. Transmission of virus during delivery through infected genital secretions from the mother
2. Focal disease – the temporal lobe is most commonly affected. This form of the disease appears in children and adults. It is possible that many of these cases arise from reactivation of virus. The mortality rate is high (70%) without treatment.

- It is of utmost importance to make a diagnosis of HSE early. It is general practice that IV acyclovir is given in all cases of suspected HSE before laboratory results are available.

Herpes Simplex Encephalitis



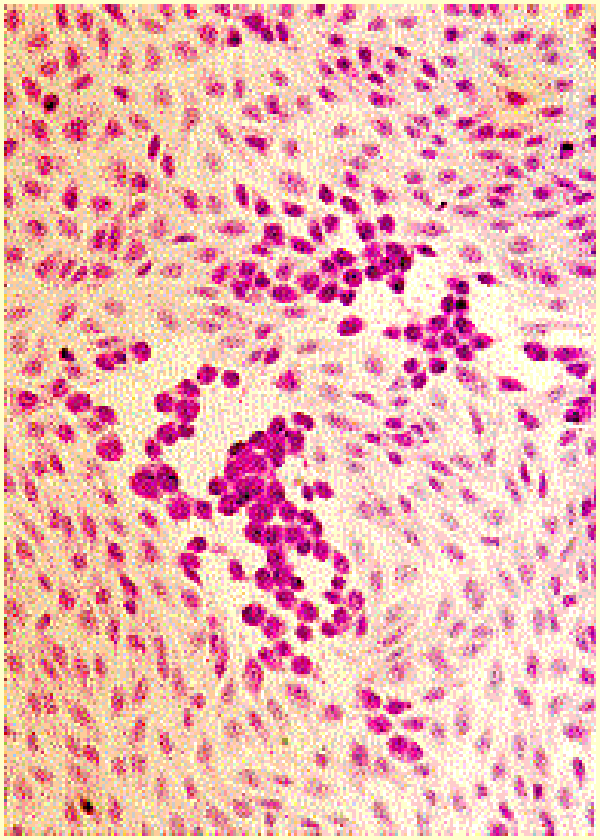
CT Scan



Autopsy

Laboratory Diagnosis

- Direct Detection
  - Electron microscopy of vesicle fluid - rapid result but cannot distinguish between HSV and VZV
  - Immunofluorescence of skin scrappings - can distinguish between HSV and VZV
  - PCR - now used routinely for the diagnosis of herpes simple encephalitis
- Virus Isolation
  - HSV-1 and HSV-2 are among the easiest viruses to cultivate. It usually takes only 1 - 5 days for a result to be available.
- Serology
  - Not that useful in the acute phase because it takes 1-2 weeks before antibodies appear after infection.
- Cytopathology
  - Multinucleated giant cells and ballooning of cells.



Cytopathic Effect of HSV in cell culture: Note the ballooning of cells.

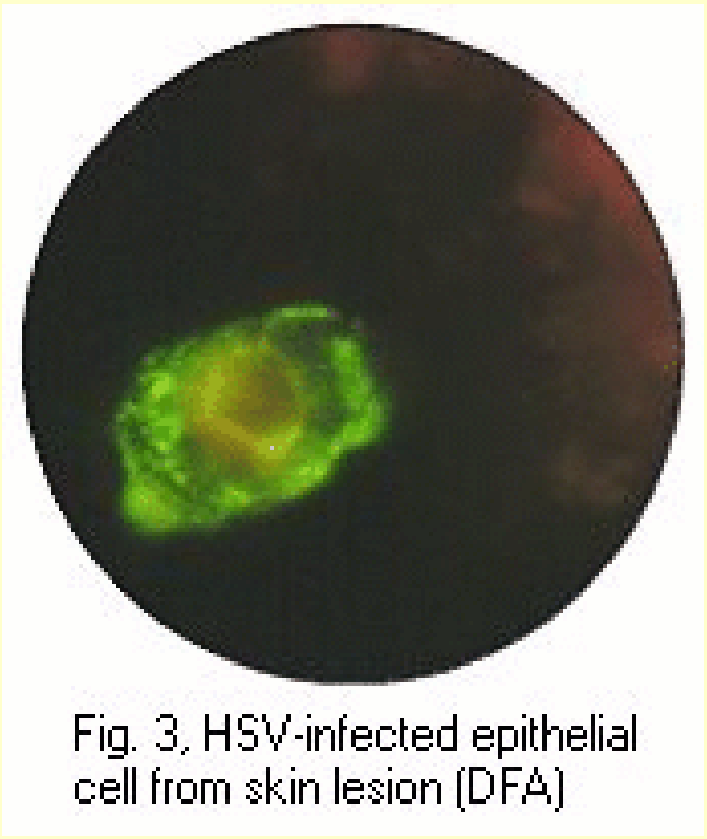


Fig. 3, HSV-infected epithelial cell from skin lesion (DFA)

Positive immunofluorescence test for HSV antigen in epithelial cell.

Management and prevention

- At present, there are only a few indications of antiviral chemo-therapy:

1. the primary infection is especially severe
2. dissemination
3. sight is threatened
4. herpes simplex encephalitis

- Acyclovir – this is the drug of choice.
- Prevention

1. Avoiding contact with individuals with lesions; however, virus may be shed asymptomatically
2. Safe sexual practices
3. Cesarean section delivery to minimize contact of the infant with infected maternal genital secretions

2- Varicella- Zoster Virus (VZV)

Epidemiology

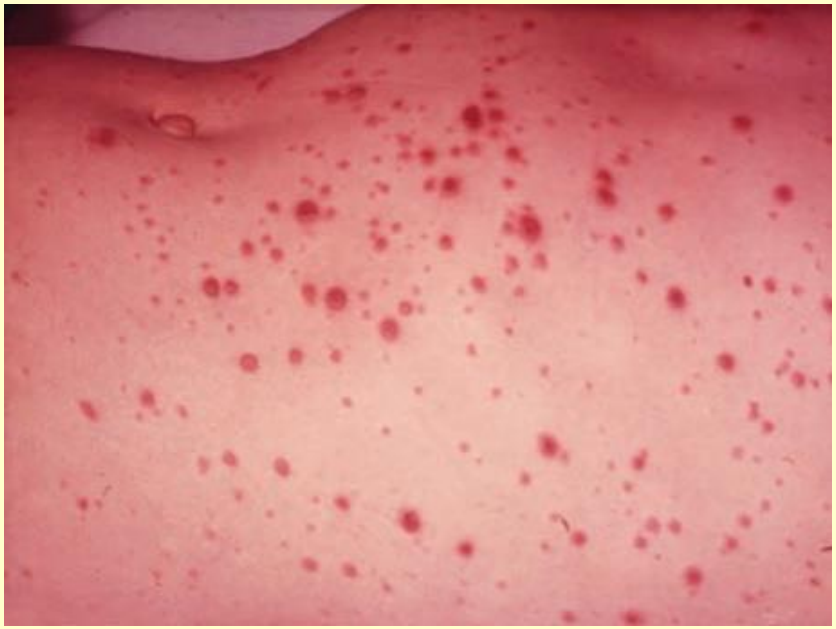
- Primary varicella is an endemic disease. Varicella is one of the classic diseases of childhood, with the highest prevalence occurring in the 4 - 10 years old age group.
- Varicella is highly communicable, with an attack rate of 90% in close contacts.
- Most people become infected before adulthood but 10% of young adults remain susceptible.

Pathogenesis

- The virus is thought to gain entry via the respiratory tract and spreads shortly after to the lymphoid system.
- After an incubation period of 14 days, the virus arrives at its main target organ, the skin.
- Following the primary infection, the virus remains latent in the cerebral or posterior root ganglia. In 10 - 20% of individuals, a single recurrent infection occurs after several decades.
- The virus reactivates in the ganglion and tracks down the sensory nerve to the area of the skin innervated by the nerve, producing a varicellaform rash in the dermatome distribution.

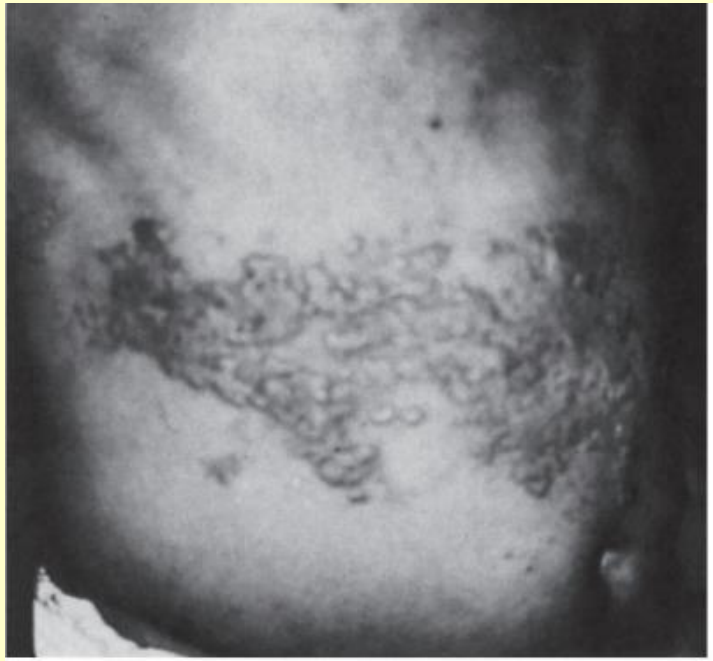
Varicella (chickenpox)

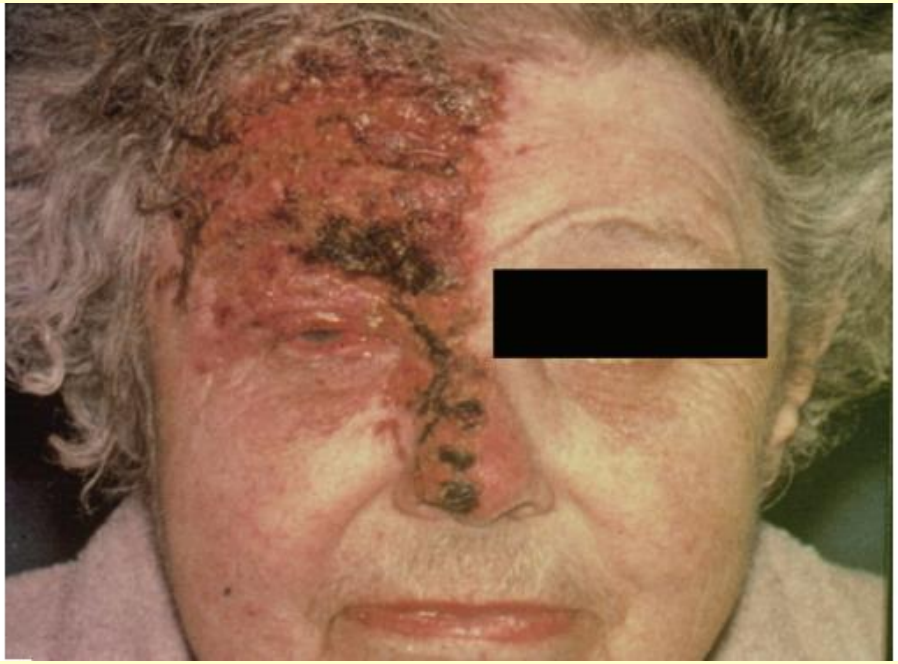
- Primary infection results in varicella (chickenpox)
- Incubation period of 14-21 days
- Presents fever, lymphadenopathy, a widespread vesicular rash.
- The rash appears first on the trunk and then on the face, the limbs, and the buccal and pharyngeal mucosa
- Successive fresh vesicles appear in crops, so that all stages of macules, papules, vesicles, and crusts may be seen at one time
- The features are so characteristic that a diagnosis can usually be made on clinical grounds alone.
- Complications are rare and may include viral pneumonia, encephalitis, and hemorrhagic chickenpox.

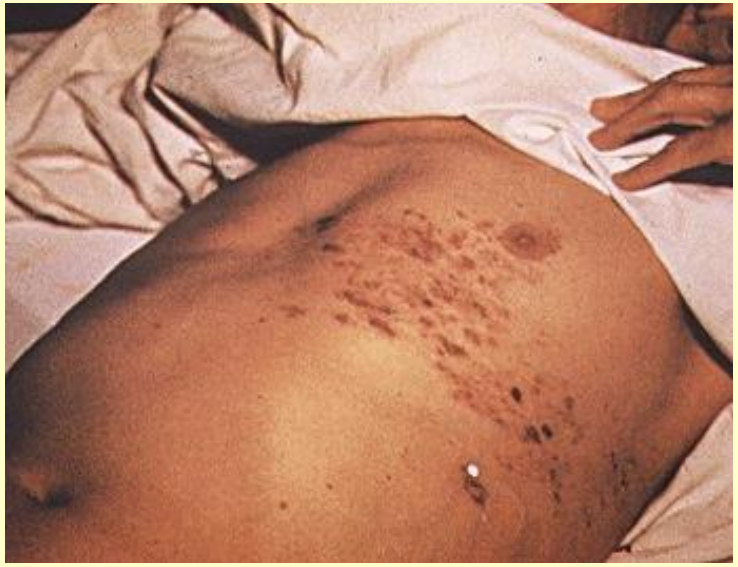


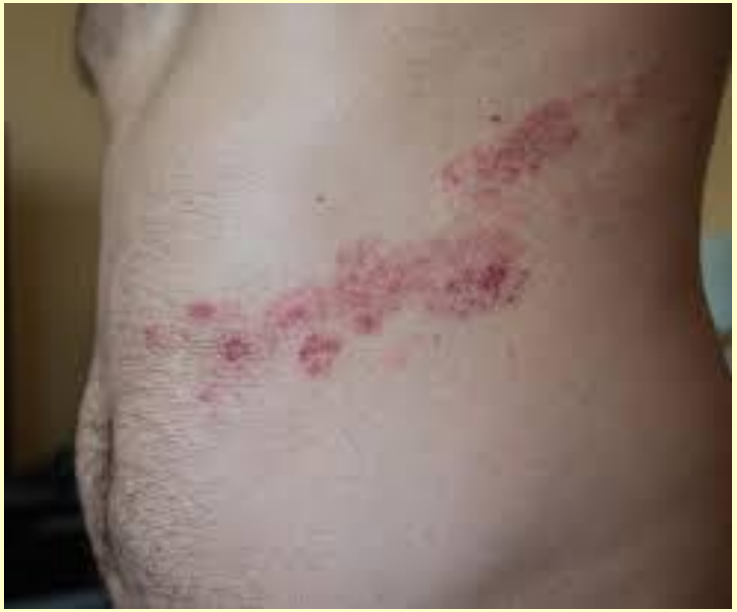
Herpes Zoster (Shingles)

- Herpes Zoster mainly affect a single dermatome of the skin.
- It may occur at any age but the vast majority of patients are more than 50 years of age.
- The latent virus reactivates in a sensory ganglion and tracks down the sensory nerve to the appropriate segment.
- There is a characteristic eruption of vesicles in the dermatome which is often accompanied by intensive pain which may last for months (postherpetic neuralgia)
- Herpes zoster affecting the eye and face may pose great problems.
- As with varicella, herpes zoster in a far greater problem in immunocompromised patients in whom the reactivation occurs earlier in life and multiple attacks occur as well as complications.
- Complications are rare and include encephalitis and disseminated herpes zoster.









Laboratory Diagnosis

The clinical presentations of varicella or zoster are so characteristic that laboratory confirmation is rarely required. Laboratory diagnosis is required only for atypical presentations, particularly in the immunocompromised.

- Virus Isolation - rarely carried out as it requires 2-3.
- Direct detection – electron microscopy for vesicle fluids and immunofluorescence on skin scrappings.
- Serology – The presence of VZV IgM is indicative of a recent primary infection. IgG is indicative of past infection and immunity.
- PCR
- Cytopathology: multinucleated giant cells

Management and prevention

- Uncomplicated varicella is a self-limited disease and requires no specific treatment. However, acyclovir has been shown to accelerate the resolution of the disease.
- Acyclovir should be given promptly to immunocompromised individuals with varicella infection and normal individuals with serious complications such as pneumonia and encephalitis.
- A live attenuated vaccine is available. Recent data suggests that the vaccine is safe
- Where urgent protection is needed, passive immunization should be given. Zoster immunoglobulin (ZIG) is the preparation of choice but it is very expensive.

3- Cytomegalovirus (CMV)

Epidemiology

- CMV is one of the most successful human pathogens, it can be transmitted vertically or horizontally usually with little effect on the host.
- Once infected, the person carries the virus for life which may be activated from time to time, especially in immunocompromised individuals, during which infectious virions 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 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 after Down's syndrome and is responsible for more cases of congenital damage than rubella

- Perinatal infection - usually asymptomatic
- Postnatal infection - 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.
- 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

- 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.
- 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

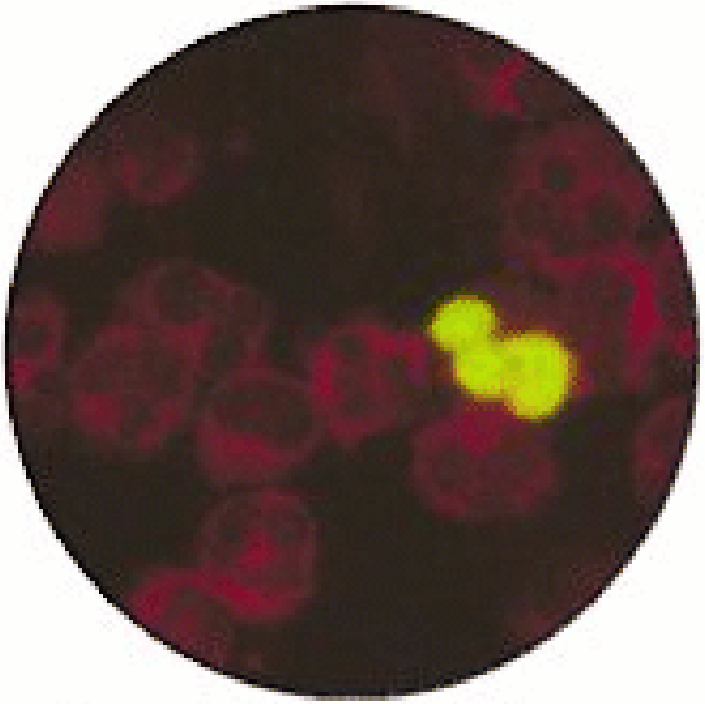


Figure 4 CMV pp65 antigens detected in nuclei of peripheral blood neutrophils

DEAFF test for CMV

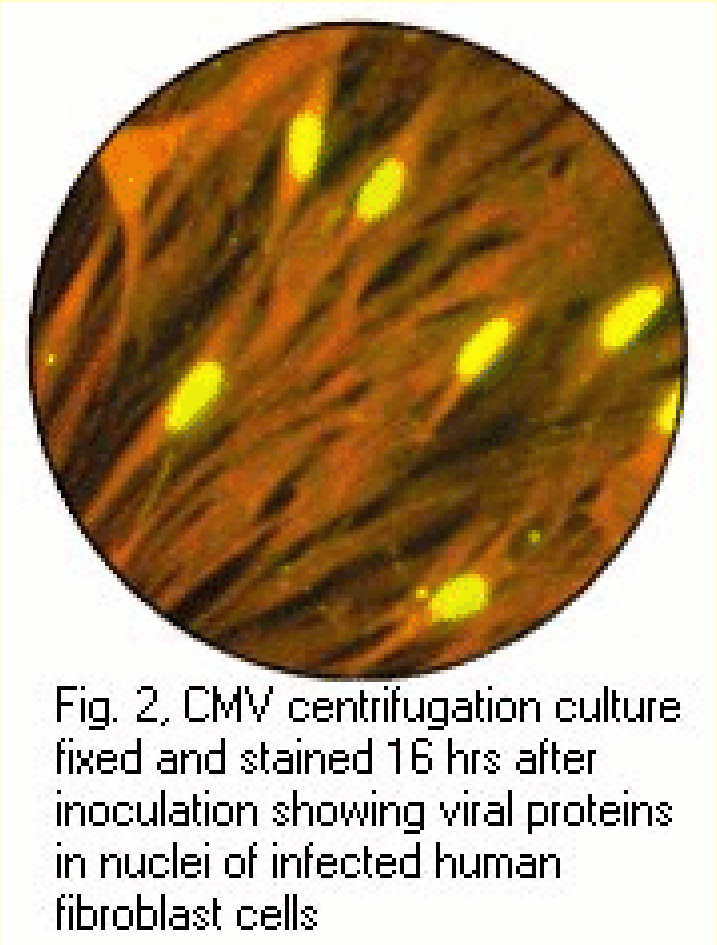
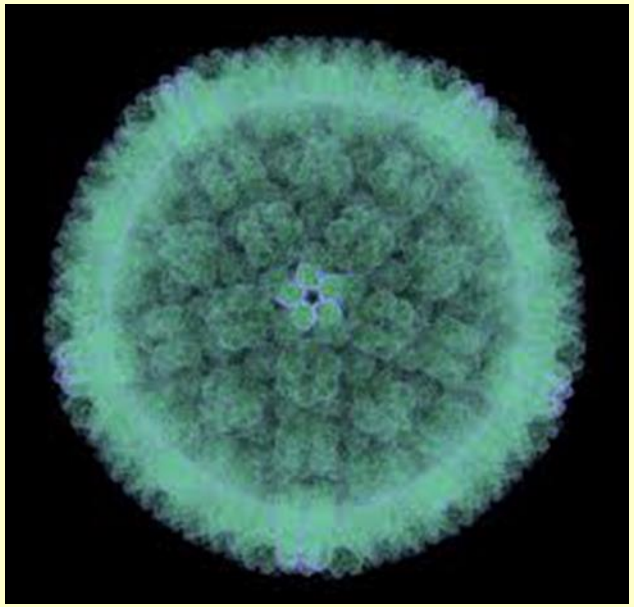


Fig. 2, CMV centrifugation culture fixed and stained 16 hrs after inoculation showing viral proteins in nuclei of infected human fibroblast cells

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.
- No licensed vaccine is available.

4- Epstein-Barr Virus (EBV)



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

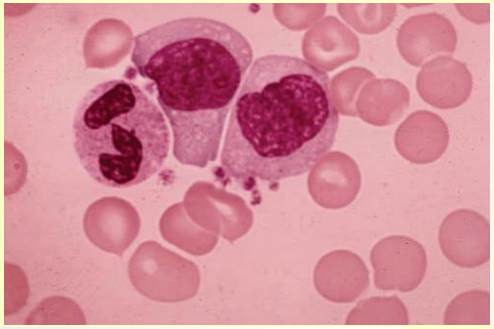
- The virus is transmitted by contact with saliva, particularly through kissing.

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.
- EBV can immortalize B-lymphocytes in vitro and in vivo
- Disease Associations:

1. Infectious Mononucleosis
2. Burkitt's lymphoma
3. Nasopharyngeal carcinoma
4. Lymphoproliferative disease and lymphoma in the immunosuppressed.

Infectious Mononuclosis



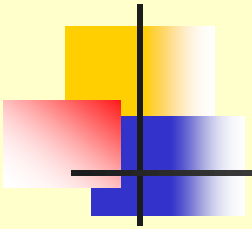
- Primary EBV infection is usually subclinical in childhood. However, in adolescents and adults, there is a 50% chance that the syndrome of infectious mononucleosis (IM) will develop.
- IM is usually a self-limited disease which consists of fever, lymphadenopathy, and splenomegaly. Atypical lymphocytes 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.

Burkitt's Lymphoma

- 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.
- In theory BL can be controlled by vaccination against EBV.

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
- 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.



5- Human Herpes Virus 6, 7, 8

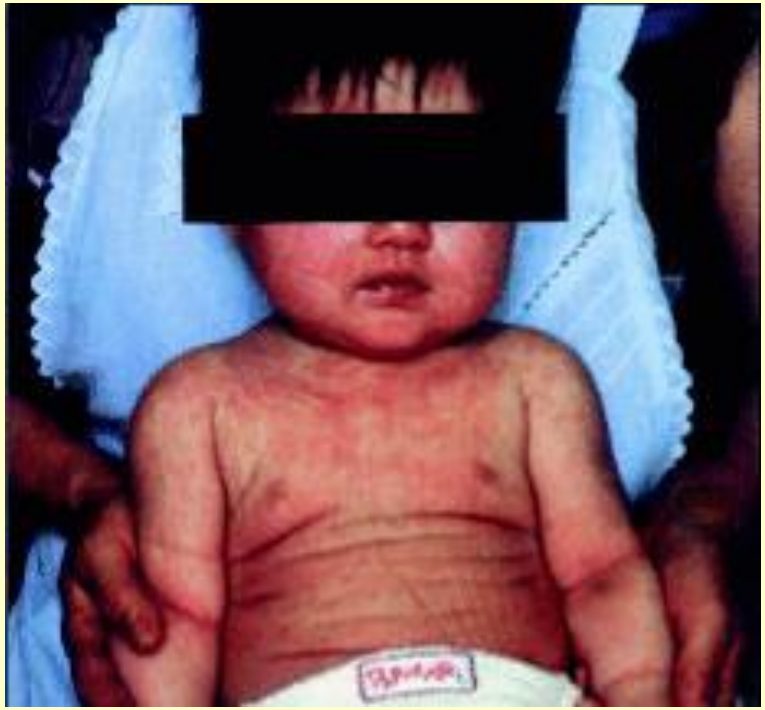
Epidemiology and Pathogenesis

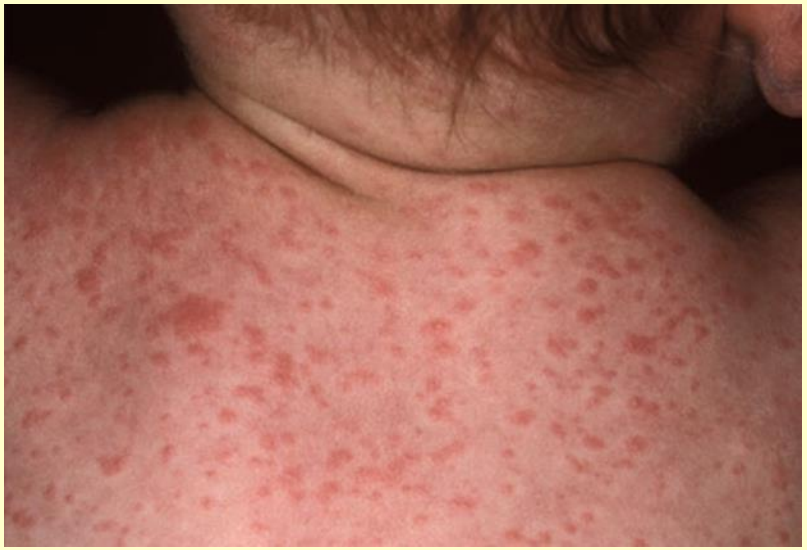
- HHV-6 and HHV-7 are found worldwide.
- They are transmitted mainly through contact with saliva and through breast feeding.
- HHV-6 and HHV-7 infection are acquired rapidly after the age of 4 months when the effect of maternal antibody wears off.
- By the time of adulthood, 90-99% of the population had been infected by both viruses.
- Like other herpesviruses, HHV-6 and HHV-7 remains latent in the body after primary infection and reactivates from time to time.
- The main target cell is the T-lymphocyte, although B-lymphocytes may also be infected.

Clinical Manifestations

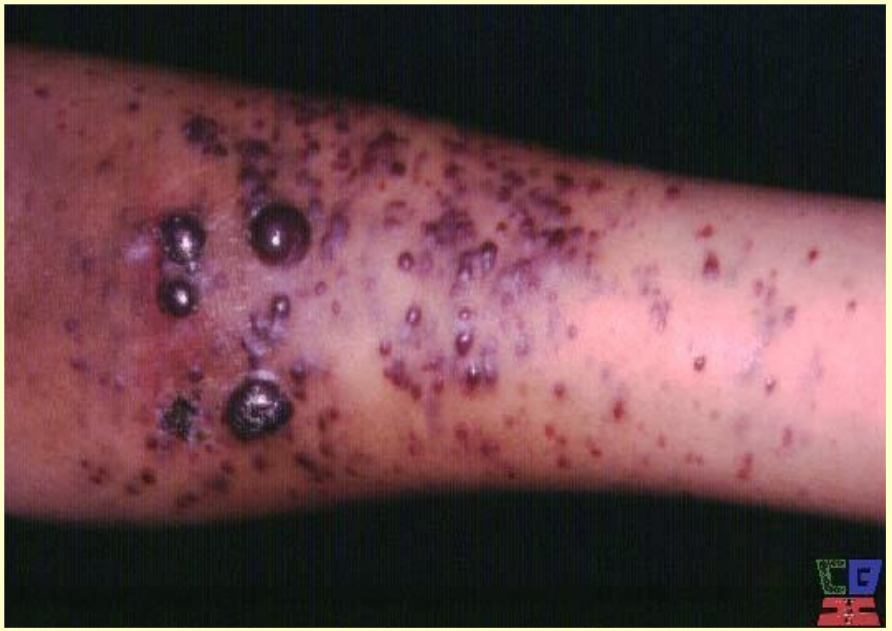
- Primary HHV-6 infection is associated with Roseala Infantum
- Most cases occur in infants between the ages of 4 months and two years.
- A spiking fever develops over a period of 2 days followed by a mild rash.
- If primary infection is delayed until adulthood, there is a small chance that an infectious 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.

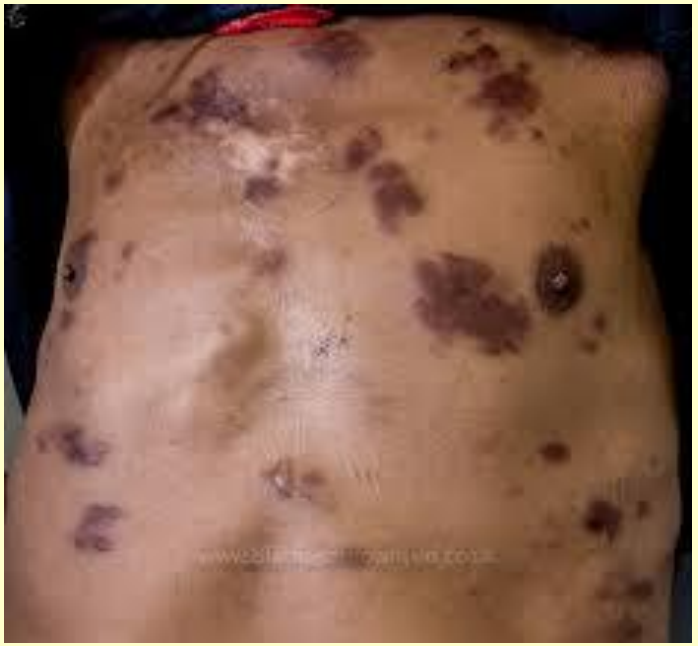
Roseala Infantum





Kaposi's Sarcoma





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.