



Virology for 2nd Year MD Students

(08) DNA viruses: *Herpesviridae* 2

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الไวروسات الحميدة
HHV-3
HHV-4
HHV-5

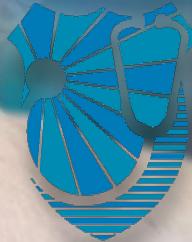
HHV-6 & HHV 7

HHV-8

الไวروس الحميدة بقلم :
dsDNA : Enveloped Latency & Reactivation
صورة المنشورة

overview

Virus	الไวروس	Tropism	Latency
Varicella Zoster Virus	HHV-3	Epithelial cells	Sensory ganglia
Epstein-Barr Virus	HHV-4	B cells, oral epithelium	B cells
Cytomegalovirus	HHV-5	Almost any cell	Myeloid cells
HHV-6	HHV-6	Many immune cells	PBMCs
HHV-7	HHV-7	CD4+ T cells	PBMCs
Kaposi's Sarcoma-Associated Herpesvirus	HHV-8	B cells	B cells



Human herpes virus 3 (HHV-3)

Varicella zoster virus (VZV)

chickenpox

حُنَّام

Dermatome ← الطفح يمتد على

- Zoster was derived from a Greek word meaning belt.
- Shingles was derived from a Latin word meaning belt.
- The virus is highly contagious.
- Tropism: Epithelial mucosal cells.
- Latency: Sensory neurons (dorsal ganglia).
- Cellular receptors: Heparan sulfate among others.

HSV ملحوظ



Human herpes virus 3 (HHV-3) Varicella zoster virus (VZV)

- Transmission: Respiratory, direct contact with lesions
- Varicella (chickenpox) is highly communicable and is a common epidemic disease of childhood (most cases occur in children under 10 years of age).
- Zoster occurs sporadically, chiefly in adults and without seasonal prevalence. Ten to 20 percent of adults will experience at least one zoster attack during their lifetime, usually after the age of 50.
↳ as a result of the death of T cell

even before symptoms appear

بشكل متقطع *خصوصاً*

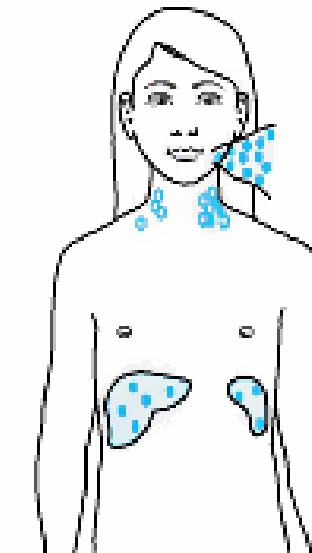




VZV

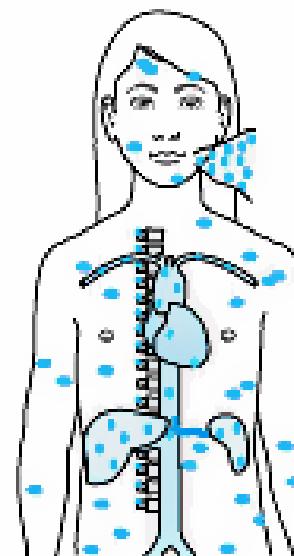
Pathogenesis & Pathology

Incubation period



- { Inoculation of respiratory mucosa
- { Viral replication in regional nodes
→ virus-infected cells into capillaries

Acute illness



- { Primary viremia
→ replication in liver/spleen

- { Secondary viremia: mononuclear cell transport to skin and mucous membranes

- { Virus release into respiratory secretions

- { Replication in epidermal cells
- { Virus in dorsal root ganglia

- { VZV specific immunity
→ resolution of replication



- Pathogenesis (مهم جداً)
Primary infection → Varicella (Chickenpox)

دخول الفيروس عبر respiratory tract
تكاثر أولي

Viremia

وصول للجلد → vesicular rash

بعدها الفيروس يدخل الأعصاب → Latency

- Latency location: dorsal root ganglia
- Reactivation → Zoster (Shingles)

يصير عند:

كبار السن

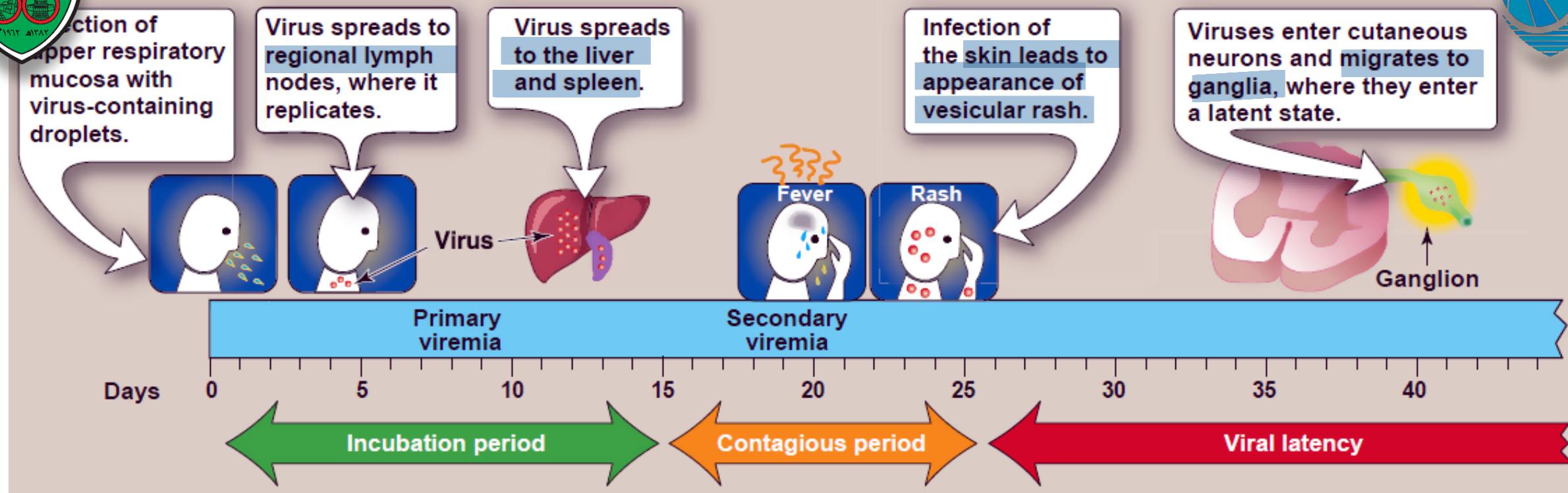
Immunocompromised

الفيروس يرجع يمشي anterograde على العصب → الجلد

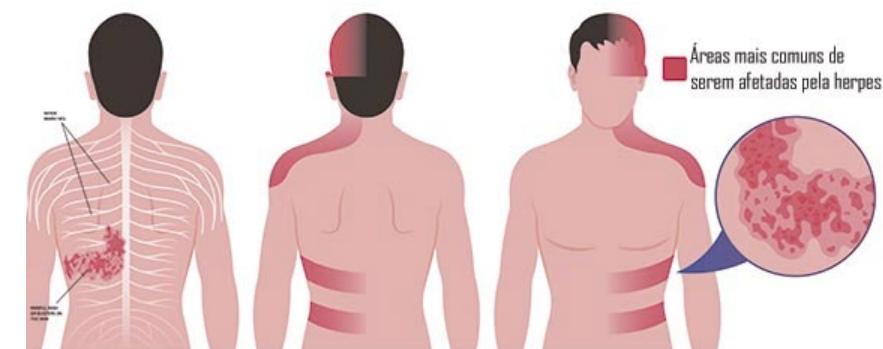
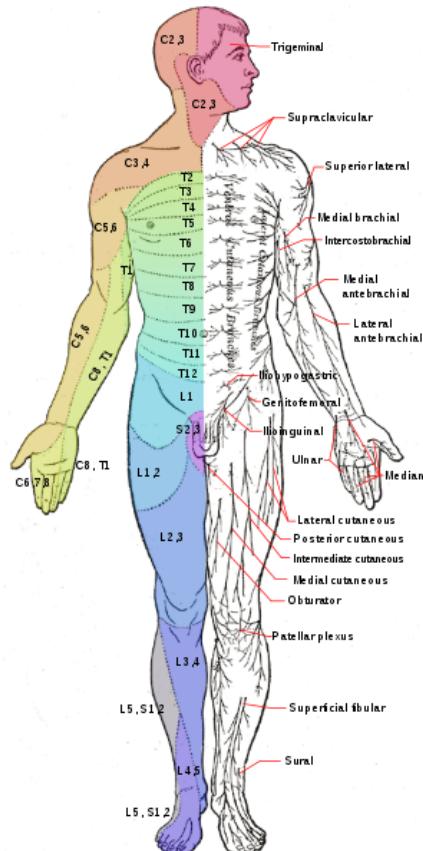
يسbib Dermatome واحد فقط

NOTE

Created by Notein



VZV Pathogenesis & Pathology



VZV Pathogenesis & Pathology

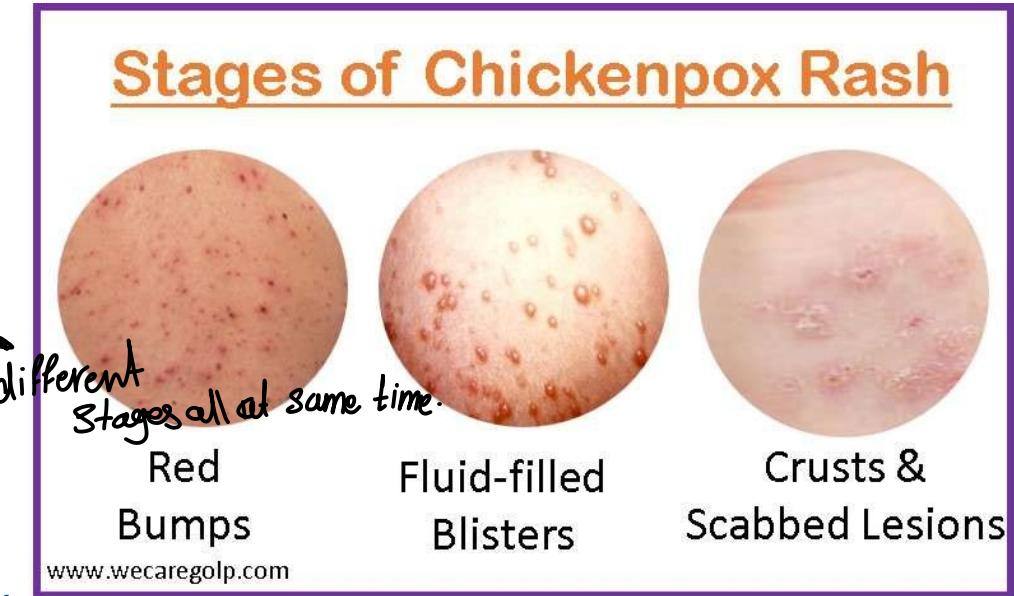


Chickenpox Clinical Features

- Subclinical varicella is unusual. *لأنه نادر*
- The incubation period: 10-21 days.
- Malaise and fever are prodromal, followed by rash, first on the trunk and then on the face, the limbs, and the mouth.
- Successive fresh vesicles appear in crops, so all stages of macules, papules, vesicles, and crusts may be seen at one time.
- The rash lasts about 5 days.
- Complications are rare in normal children, and the mortality rate is very low.

asymptomatic
which is very rare.

Mentioned in
the previous file.



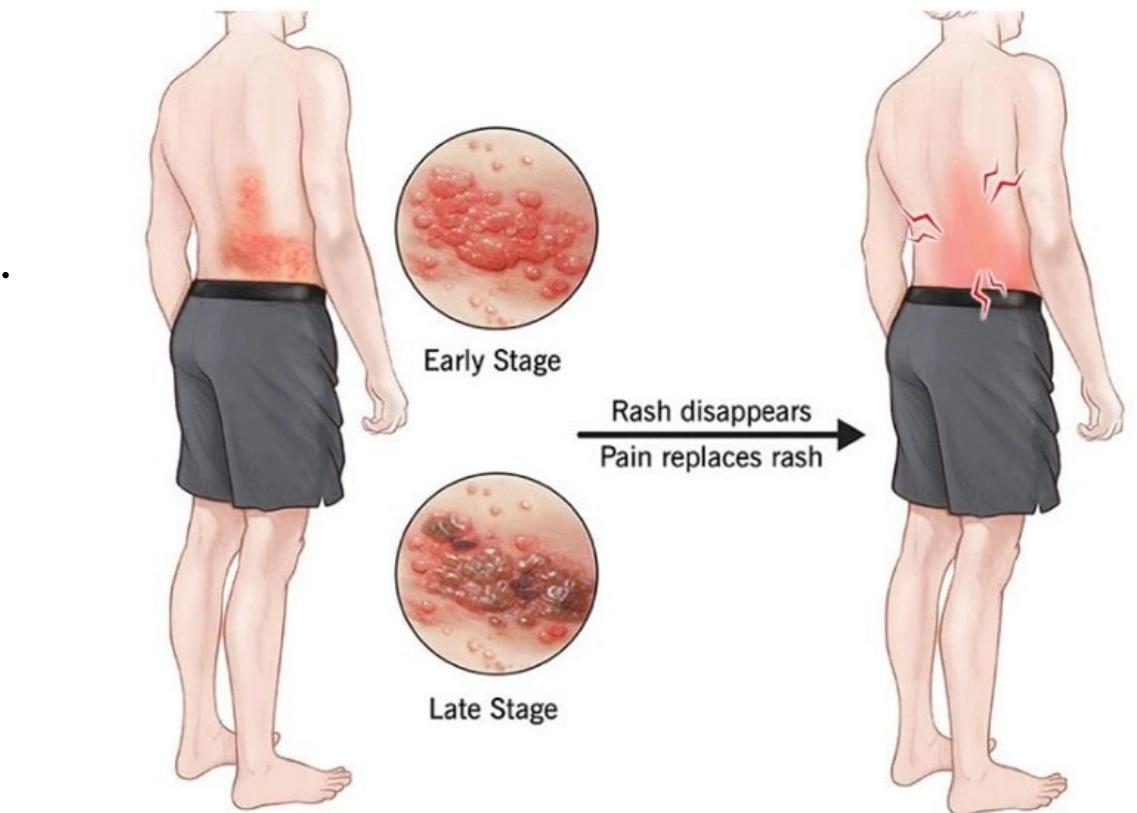
* in SmallPOX the lesions are present as macules & then papules all of ^{NOTE} lesions



Zoster Clinical Features

- Zoster occurs in immunocompromised persons.
- It starts with severe pain in the area of skin or mucosa supplied by the sensory nerves and ganglia.
قبل اتفاق *الى مدار فيه* *reactivation*
- Within a few days, a crop of vesicles appears over the skin supplied by the affected nerves.
- The **trunk, head, and neck** are most commonly affected. *Common sites*
- The most common complication of zoster in the elderly is **postherpetic neuralgia** which is a protracted pain that may continue for months.

Post Herpetic Neuralgia



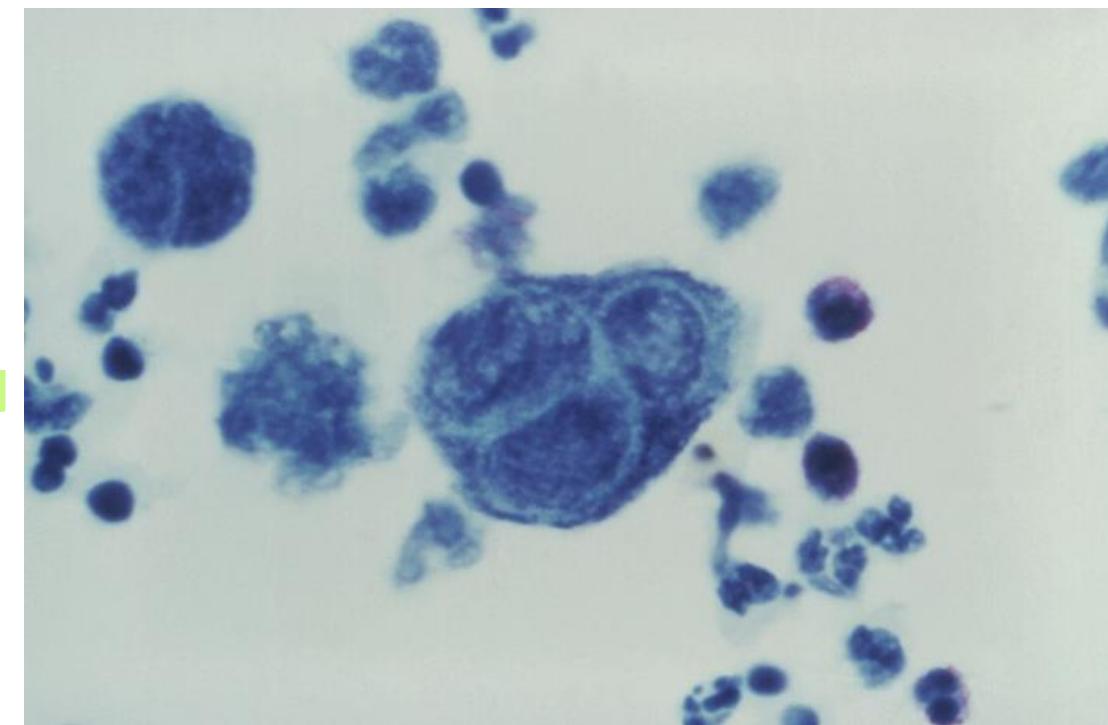
ألم مزمن شingles Infection
nerve pain following
herpes

Postherpetic Neuralgia



VZV – Diagnosis, Treatment, and Prevention

- Diagnosis: Clinical, Tzanck smear, Serology, PCR.
- Varicella in normal children is a mild disease and requires no treatment.
- Acyclovir can prevent the development of systemic disease in varicella-infected immunosuppressed patients and can halt the progression of zoster in adults.
- A live attenuated varicella vaccine is highly effective at inducing protection from varicella in children (80–85% effective), but less so in adults (70%).
- Varicella infections can occur in vaccinated persons, but they are usually mild illnesses.
- Zoster vaccine is indicated for prevention of shingles in adults ≥ 50 years.





Epstein-Barr Virus (EBV)

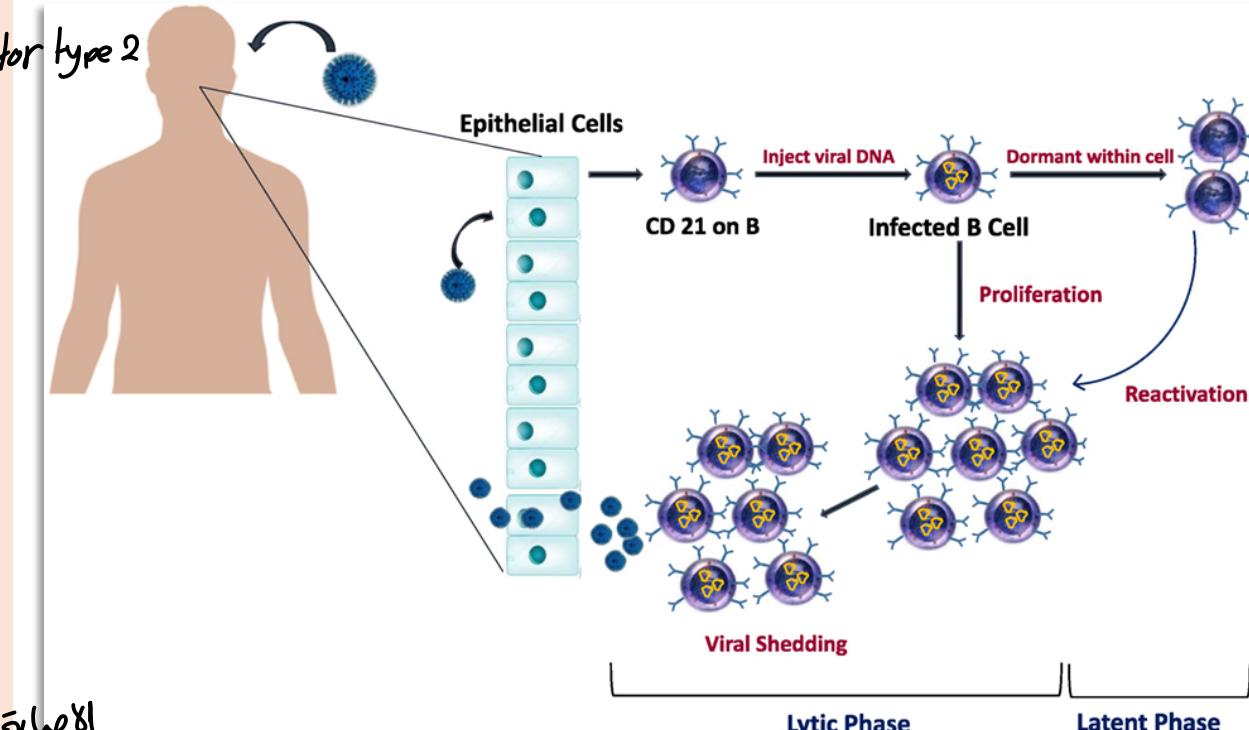
↳ *Oncovirus*

other subtypes

Which one? Gamma Herpesvirus.

- Tropism: B cells, oral epithelial cells.
- Latency: B cells.
- Cellular receptors: CR2 (CD21). *Complement receptor type 2*
- Transmission: Contact with oropharyngeal secretions, saliva.
- In developing countries, infections occur early in life; more than 90% of children are infected by age 6. *كلما كان العرق أقل احتمالاً يظهر المرض الأعراض بتجدد أقل* *asymptomatic*
- These infections in early childhood usually occur without any recognizable disease.
- The inapparent infections result in permanent immunity to infectious mononucleosis.

development of cancers



دائم خص
بعض مناعة
غير خارجة
لا صدمة بالجسم



Infectious Mononucleosis (IM)

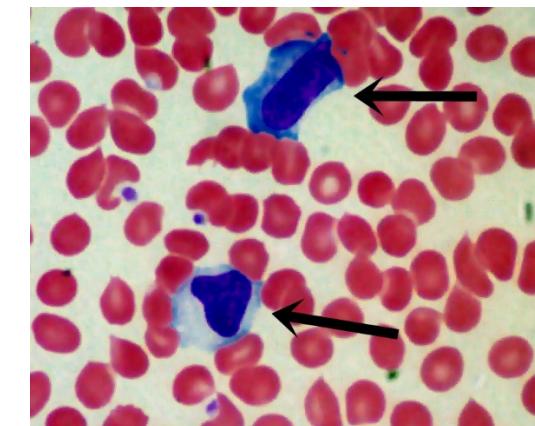
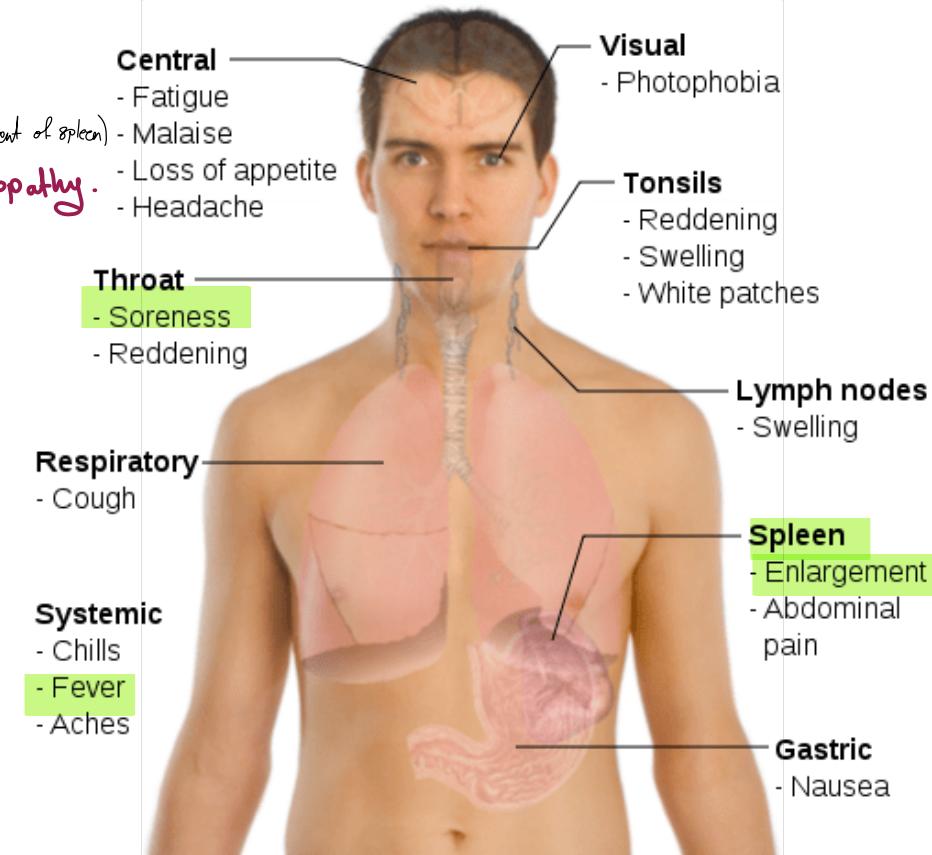
The incubation period for IM is about 4 to 6 weeks.

The peripheral blood shows leukocytosis, an increase in T cells but not B cells, and atypical  lymphocytes (predominantly activated T cells having large amounts of cytoplasm). 

Clinical Features (The doctor mentioned)

- Fever
- Sore throat
- Fatigue
- Splenomegaly (enlargement of spleen)
- Cervical Lymphadenopathy.

Main symptoms of **Infectious mononucleosis**





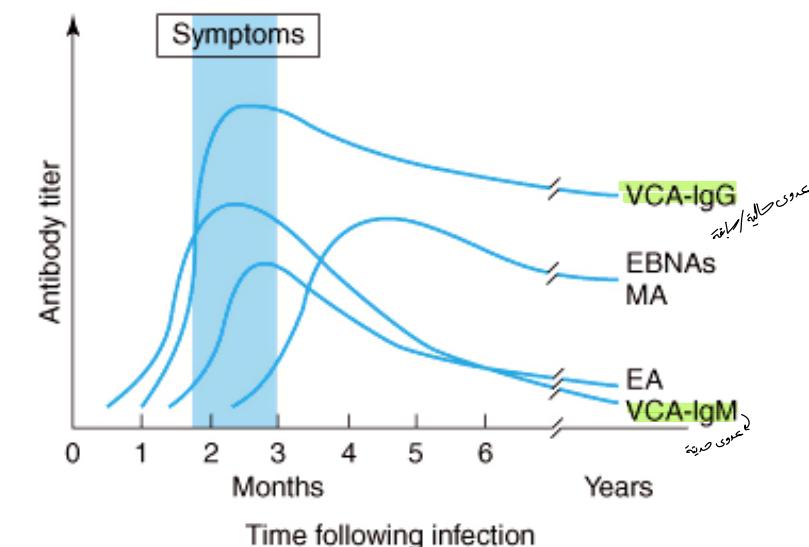
Cancers Associated with EBV Latent Gene Expression

من كل الناس اللي عرضهم EBV يعابوا \rightarrow Cancer

Disease	EBERs	EBNA-1	EBNA-2	LMP-1	LMP-2
Burkitt lymphoma	+	+	-	-	-
Nasopharyngeal carcinoma	+	+	-	+	+
Hodgkin disease	+	+	-	+	+
Peripheral T-cell lymphoma	+	+	-	+	+
Lymphoproliferative disease	+	+	+	+	+

IM Laboratory Diagnosis and Rx

- The diagnosis of IM in patients with typical symptoms is made by a **positive heterophile antibody**.
- Titers of **EBV-specific antibodies** (VCA, EA, MA and EBNA) are measured.
- **PCR** Detection of EBV DNA in the blood can be **useful for diagnosis of IM** if **serologic results are equivocal**.
- Treatment of IM is **supportive**. Contact sports should be avoided during the acute phase of the disease due to the risk of **splenic rupture**.



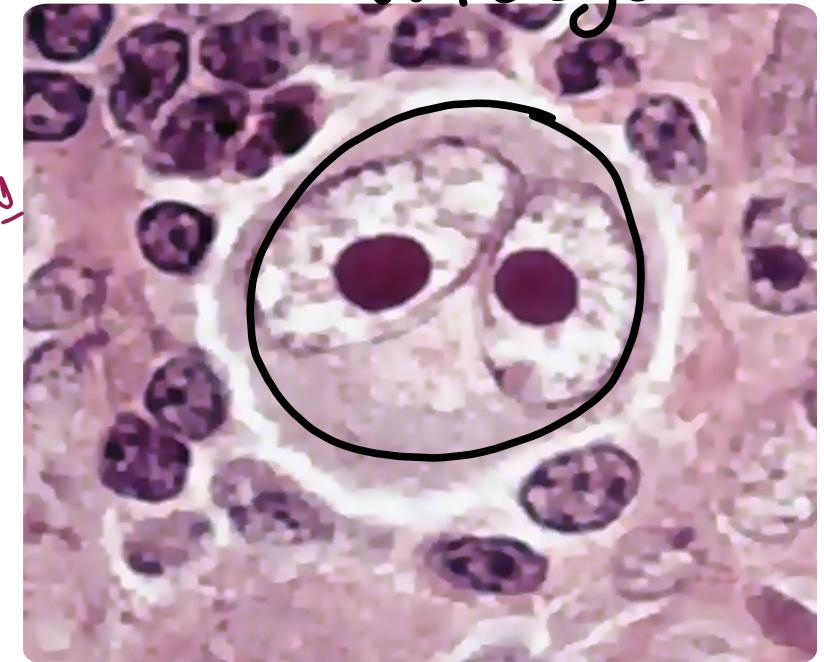


Cytomegalovirus (CMV)

الفروس المفخخ للخلايا

نغيرياً كل أنواع الخلايا

- Tropism: Epithelial cells, endothelial cells, fibroblasts, smooth muscle cells, parenchymal cells and connective tissue, cells of virtually any organ and various hematopoietic cell types.
- Latency: Myeloid cells.
related to bone marrow
- Transmission: Contact with urine, saliva, congenital, sexual.
↳ mother to fetus
- CMV is the most common congenital viral infection in the developed world, with an overall birth prevalence of approximately 0.6%.
- CMV causes IM-like syndrome in primary infection.
IM بفيروس CMV
Negative ← heterophile antibody



owl's eye inclusion





CMV in Immunocompromized Host

Congenital CMV

- Pneumonia is a frequent complication.
- CMV often causes disseminated disease (من disbatic في الجسم) in untreated AIDS patients.
- Gastroenteritis and retinitis are common problems, the latter often leading to progressive blindness.
stomach & intestines
- Approximately 10% of congenitally infected infants have signs and symptoms of disease at birth.
- Symptomatic infants have a high risk for subsequent neurologic *complications*, including hearing loss, mental retardation, microcephaly, development delay, seizure disorders, and cerebral palsy.
- The cornerstone of antiviral therapy is ganciclovir.





CMV Laboratory Diagnosis

- PCR assays have replaced virus isolation for routine detection of cytomegalovirus infections. Cell culture methods of viral isolation are too slow to guide Rx.
→ very slow
- CMV produces a characteristic CPE (Massively enlarged "cytomegalic" cells are typical, besides Owl's eye appearance of inclusion bodies "intranuclear basophilic inclusions").
→ cytopathic effect.
الفيروس يسبب التأثير الضار
نَسْخَةُ العَيْنَةِ
- Blood and urine are most commonly tested.
- Serology: Detection of viral IgM antibodies suggests a current infection.
أنت تجري بحالتي بالحالات الحالية

→ If it was positive it means

الشخص مصاب حالياً/صحيحاً

PCR
→ The best
NOTE: Created by Notein



Roseola viruses HHV-6 and HHV-7



- Both HHV-6 and HHV-7 are causative agents of roseola infantum (exanthem subitum), although infection with HHV-7 is more frequently asymptomatic.
- HHV-6 exists in two variants, HHV-6A and HHV-6B.
- Transmission: Respiratory, direct contact.
- Tropism: HHV-6: T cells, B cells, natural killer (NK) cells, Monocytes-macrophages, epithelial cells and nerve cells. HHV-7: CD4+ T lymphocytes and epithelial cells of salivary glands
- Latency: Peripheral blood mononuclear cells (PBMCs).
- Cellular receptors: HHV-6: CD46. HHV-7: CD4.

Rash
fever &
small rashes.

جامعة الاردن

Same receptor for Measles Virus

That's why it's associated with aseptic meningitis in a very small number, that's why the panel of PCR detect the causes of A. meningitis and enterov.

HSVs &
HHV-6

عدة يعفن الحالات
بسبب
A. Meningitis



Exanthem Subitum (Roseola Infantum, Sixth Disease)

درجة الحرارة تتكون عاليّة جداً، ممّن يشكّ أنه bacterial inf. أو viral أو مختلط من بين

* قبل ظهور Rash

- In the classic presentation, an infant develops sudden fever, which lasts for a few days, followed immediately by a rash that appears on the trunk and face and spreads to lower extremities as the fever subsides.
- Due to the high fever, ES might be associated with febrile seizures.
- The disease is nearly always harmless, characterized by sudden onset with high fever and manifests as a typical exanthem in small children.
- Reports of HHV-6-caused illness in adults are rare and the clinical pictures described resemble mononucleosis (EBV-negative mononucleosis).

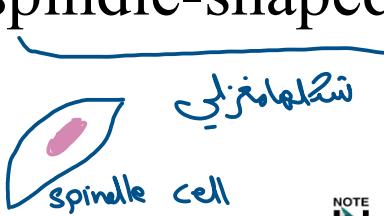


• reactivation
• في: اصابة بغير
• immunocompromised
• حالات اذيفن خفيفة
• IM-like illness



Kaposi's Sarcoma-Associated Herpesvirus

Gamma Herpes subfamily.

- Tropism: B lymphocytes. 
- Latency: B lymphocytes. 
- Transmission: Sexual contact, saliva
- Some infections are acquired early in life by nonsexual routes, possibly through contact with oral secretions. 
- It appears to be sexually transmitted among gay men, who have a higher seroprevalence compared to the general population. 
- Kaposi's sarcoma (KS) seems to originate from the viral modified pluripotent mesenchymal cells of the connective tissue transformed in spindle-shaped KS cells. 

التي عند هم
عند مصابها أن تجري
of developing
of Kaposi's
Sarcoma



Kaposi Sarcoma

في أي منطقة بالجسم:
internal organ :
Skin , or anywhere else .

↑ raised lesion
Larger than 1cm

- Nodular lesions of variable colors affecting the skin, mouth, GI tract or respiratory tract.

- Four classes of KS including:
حول البصري الاسترض التوعي
✓ Classic KS.

Its course is somewhat long
So the individual die from it

الجلد في المسن

- ✓ Endemic or African KS.

- ✓ Iatrogenic KS associated with immunosuppressive therapies in transplant patients.

- ✓ Epidemic or AIDS-related KS.
AIDS / HIV



HHV-8

- **Primary effusion lymphoma (PEL)**, which is an expansion of B cells predominantly in serosal cavities such as the pericardium, ^{حول القلب} pleura, ^{البص} and peritoneum. ^{العل} ^{دائل هذه التجاويف} ^{Lymphoma}
- **Multicentric Castleman's disease (MCD)**. MCD is a rare, polyclonal, ^{أكثرون خلايا فقارية} lymphoproliferative disease that can develop in both **HIV-negative** and **HIV-positive** individuals. ^{من بروتينات مختلفة} ^{ف�ة في العامة} ^{populat}
- KS incidence is 1 in 100,000 in the general population, whereas in **HIV-infected** individuals, the incidence is around 1 in 20. ^{KS = خضر عالي} ^{خطف ابناء}
- Diagnostic confirmation of KS is done through histopathology.
- Confirmation is done by immunohistochemistry in tissues using monoclonal antibodies to the KSHV. ^{If positive means the diagnosis is confirmed}
- Rx: HAART can induce AIDS-KS regression. Isolated lesions are treated with radiotherapy. Systemic chemotherapy is useful for the treatment of disseminated disease. ^{العمر} ^{العمر}

Virus	Disease(s)	Transmission	Tropism (Target cells)	Latency	Key Clinical Features	Diagnosis	Treatment / Prevention
Varicella Zoster Virus (VZV)	Chickenpox (primary), Zoster/Shingles (reactivation)	Respiratory, direct contact	Epithelial cells	Sensory (dorsal root) ganglia	Chickenpox: generalized vesicular rash (different stages) • Zoster: painful dermatomal rash, post-herpetic neuralgia	Clinical, PCR, Tzanck	Acyclovir (adults, immunocompromised) • Varicella & Zoster vaccines
Epstein–Barr Virus (EBV)	Infectious mononucleosis, lymphomas, NPC	Saliva	B cells, oral epithelium	B cells	IM triad: fever, pharyngitis, posterior cervical lymphadenopathy • Splenomegaly	Heterophile Ab (Monospot), EBV Abs, PCR	Supportive only • Avoid contact sports
Cytomegalovirus (CMV)	Congenital CMV, IM-like illness, severe disease in immunocompromised	Urine, saliva, sexual, congenital	Almost any cell	Myeloid cells	Congenital: hearing loss, microcephaly • AIDS: retinitis, pneumonia, GI disease	PCR, Owl's eye inclusions, IgM	Ganciclovir
HHV-6	Roseola infantum (sixth disease)	Respiratory, contact	T, B, NK cells, monocytes, epithelial, nerve cells	PBMCs	High fever → fever subsides → rash • Febrile seizures	Usually clinical	Supportive
HHV-7	Roseola (often asymptomatic)	Respiratory, contact	CD4+ T cells, salivary glands	PBMCs	Similar to HHV-6 but milder / asymptomatic	Usually clinical	Supportive
Kaposi's Sarcoma-Associated Herpesvirus (HHV-8)	Kaposi sarcoma, PEL, Castleman disease	Sexual, saliva	B lymphocytes	B lymphocytes	KS: purple nodular lesions (skin, oral, GI) • ↑ risk in HIV	Histopathology + IHC	HAART, radiotherapy, chemotherapy NOTE: Created by Notein



**Thank You...
Wishing you all the best!**