Infectious Mononucleosis.

- Infectious Mononucleosis (**IM**; also known as **EBV infectious mononucleosis** or **glandular fever** and sometimes as the **kissing disease** from its oral transmission or simply as **mono** in North America and as **glandular fever** in other English-speaking countries) is an infectious, widespread viral disease caused by the Epstein-Barr virus (EBV).

Infectious Mononucleosis: Cause

- EBV 90% of acute IM
- Etiology of most EBV-negative IM: unknown
- Other Herpesviruses:
  - Cytomegalovirus (CMV)
  - herpes simplex 1 and simplex 2
  - human herpesvirus 6
- Other viruses:
  - adenovirus
  - hepatitis A, hepatitis B, or hepatitis C
  - rubella
  - primary human immunodeficiency virus in adolescents or young adults.

VIROLOGY.

- Epstein Barr Virus (EBV)
  - Herpes Family – (linear DNA virus HHV4)
  - Surrounded by nucleocapsid and glycoprotein envelope
- Also associated with nasopharyngeal carcinoma, Burkitts lymphoma, Hodgkins Disease, B cell lymphoma.

Epidemiology: Incidence

- Population-based studies; 90% of population have been infected or have antibodies to the virus.
- Highest incidence rates: 15-19 years.
- No seasonal predilection.
- Higher rate in persons of white race than in other ethnic groups.

Primary EBV infection: Seroprevalence

- In developing countries -80-100% of children becoming infected by 3-6 yrs. of age
  - clinically silent or mild disease.
- In developed countries
  - occurs later in life, 10-30 years of age
  - induce clinically mononucleosis syndrome

Epidemiology: Transmission

- Incubation period: 30 – 50 days.
  (shorter in young children)
- Oral secretion
  - major role but occur slowly
- Blood products, Transplanted organs
  - less commonly than CMV
- Intrauterine
  - infrequently
  - if infected; no adverse fetal outcomes and no viral transmission to the fetus.

Pathophysiology

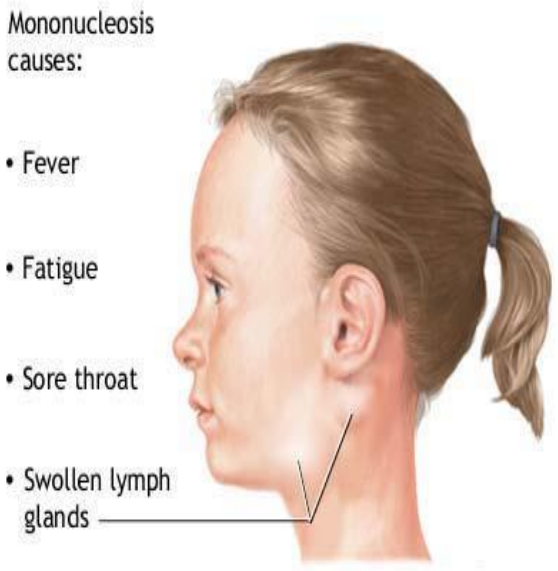
- Reservoir of EBV: Humans only.
- EBV founds in the saliva for the first 12-18 months after acquisition.
- Viral replication
  - Lympho-reticular system
  - liver
  - spleen
  - B lymphocytes in peripheral blood.
- Host immune response to the viral infection
  - atypical lymphocytes.
- After acute EBV infection, latently infected lymphocytes and epithelial cells persist and are immortalized.
- During latent infection, the virus is present in the lymphocytes and oropharyngeal epithelial cells as episomes in the nucleus.

Molecular Biology: EBV Subtype

- 2 subtypes
  - EBV-1 (type A): Western countries
  - EBV-2 (type B): less virulence
- In immunocompromised persons: co-infection both type 1 and type 2 strains
- No one subtype is responsible for specific lymphoproliferative diseases (geographic differences)

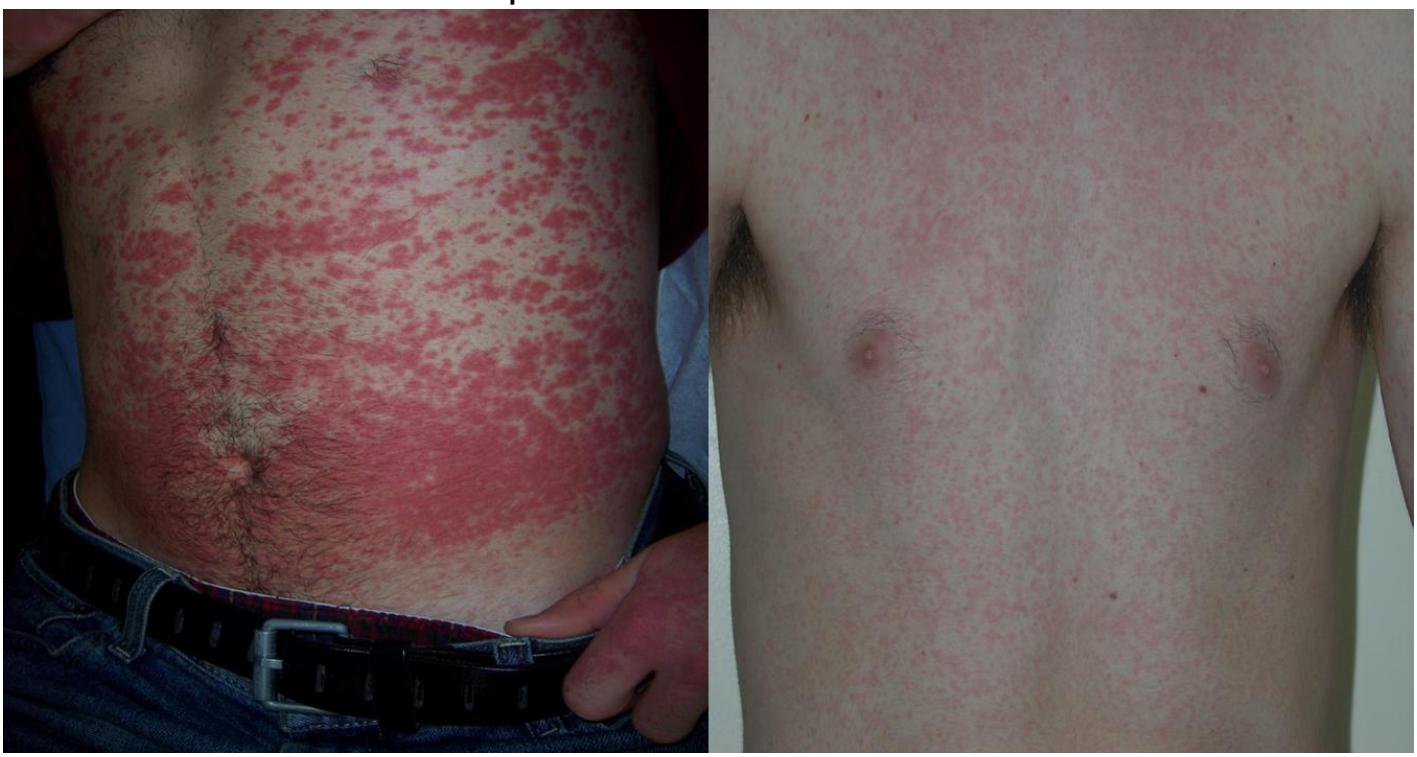
Symptoms.

- Acute infectious mononucleosis
  - fatigue and malaise 1-2 wks.
  - sore throat, pharyngitis
  - retro-orbital headache
  - fever
  - myalgia
  - nausea
  - abdominal pain
  - generalized lymphadenopathy
  - hepatosplenomegaly



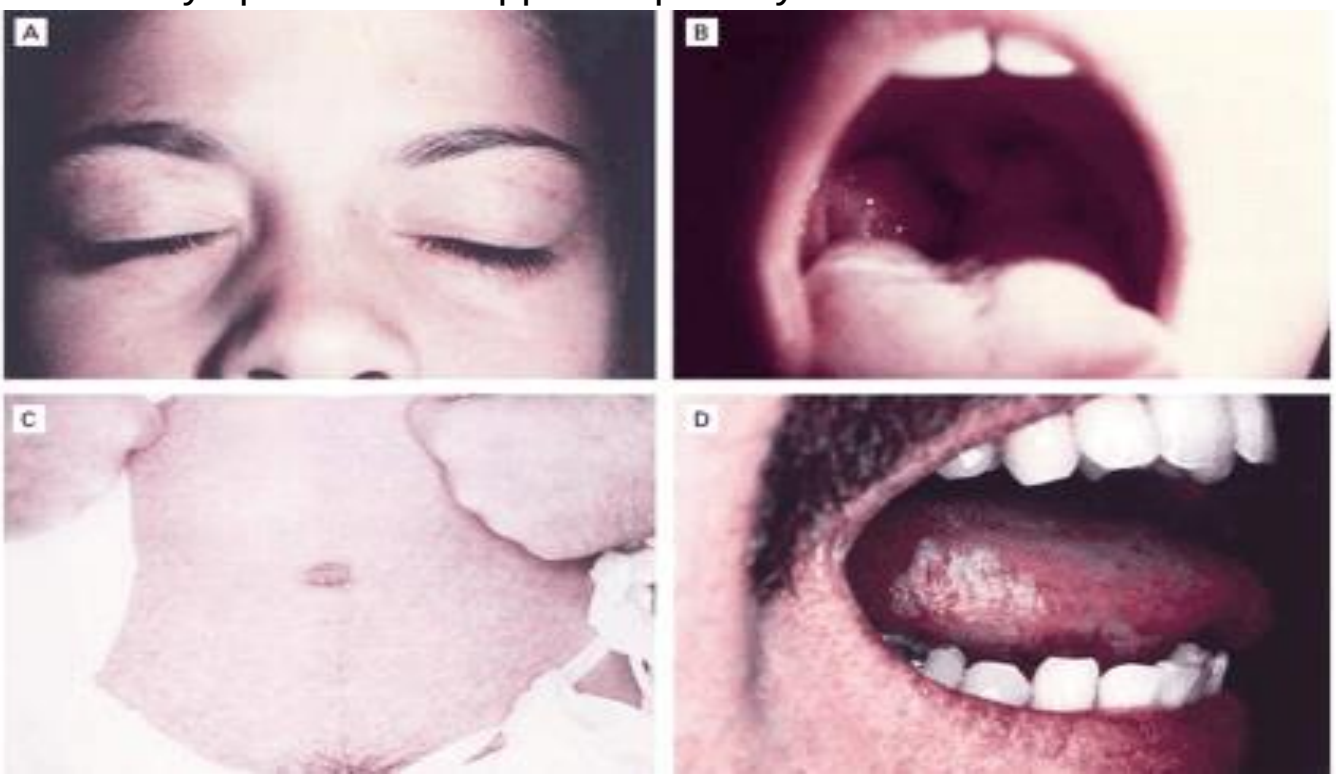
- Pharyngitis is the most consistent physical finding.
  - 1/3 of patients: exudative pharyngitis.
  - 25-60% of patients: petechiae at the junction of the hard and soft palates.
  - Tonsillar enlargement can be massive, and occasionally it causes airway obstruction.
- Lymphadenopathy: 90%
  - symmetrical enlargement.
  - mildly tender to palpation and not fix.
  - posterior cervical lymph nodes.
  - anterior cervical and submandibular nodes.
  - axillary and inguinal nodes.
  - *Enlarged epitrochlear nodes are very suggestive of infectious mononucleosis.*

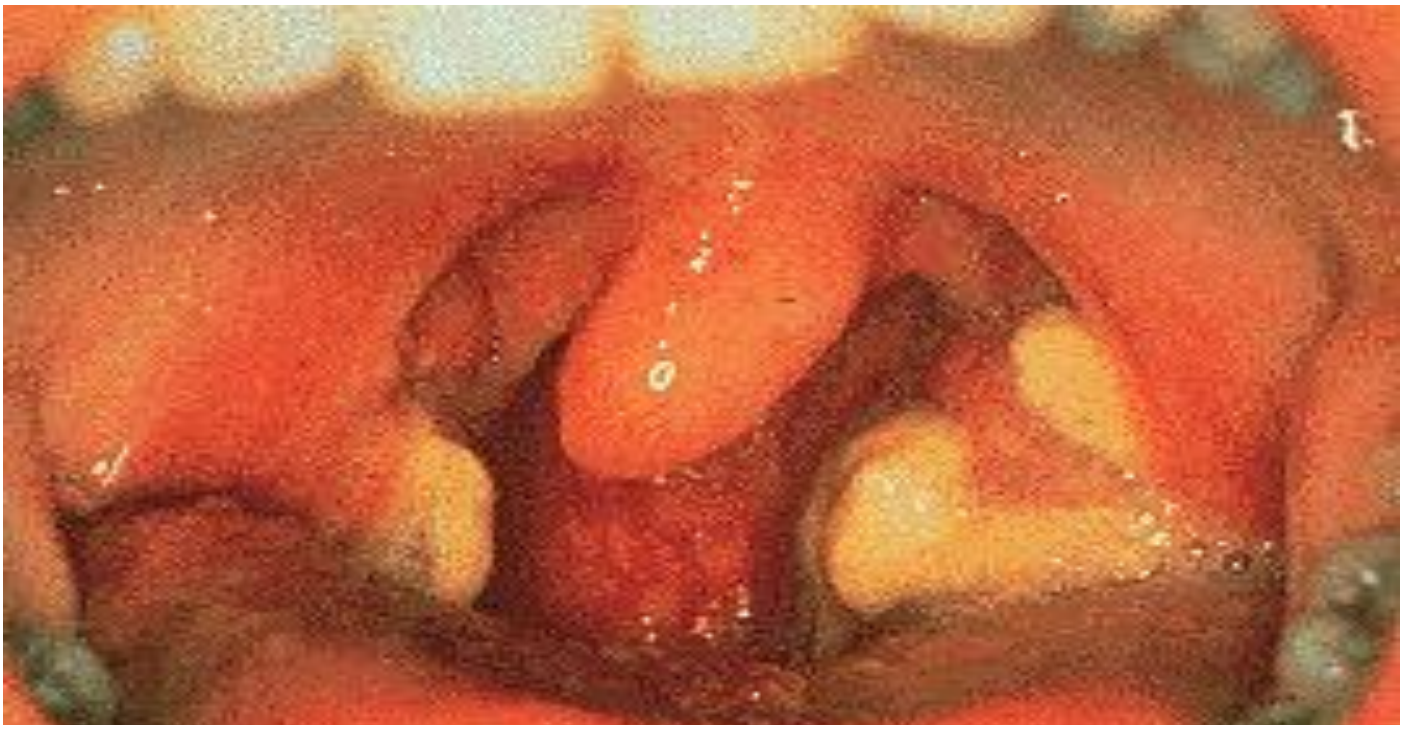
- Hepatomegaly: 60%
  - jaundice is rare.
  - Percussion tenderness over the liver is common.
- Splenomegaly: 50%
  - palpable 2-3 cm below the left costal margin and may be tender.
  - rapidly over the first week of symptoms, usually decreasing in size over the next 7-10 days.
  - spleen can rupture from relatively minor trauma or even spontaneously.
- Maculopapular rash: 15%
  - usually faint, widely scattered, and erythematous
  - occurs in 3-15% of patients and is more common in young children.
  - 80% of patients, treatment with amoxicillin or ampicillin is associated with rash
  - Circulating immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies to ampicillin are demonstrable.



IM with rash after treatment with amoxicillin or ampicillin

- Eyelid edema: 15%
  - may be present, especially in the first week
- Children younger than 4 years: more commonly
  - splenomegaly or hepatomegaly
  - rash
  - symptoms of an upper respiratory tract infection





Exudative pharyngotonsillitis

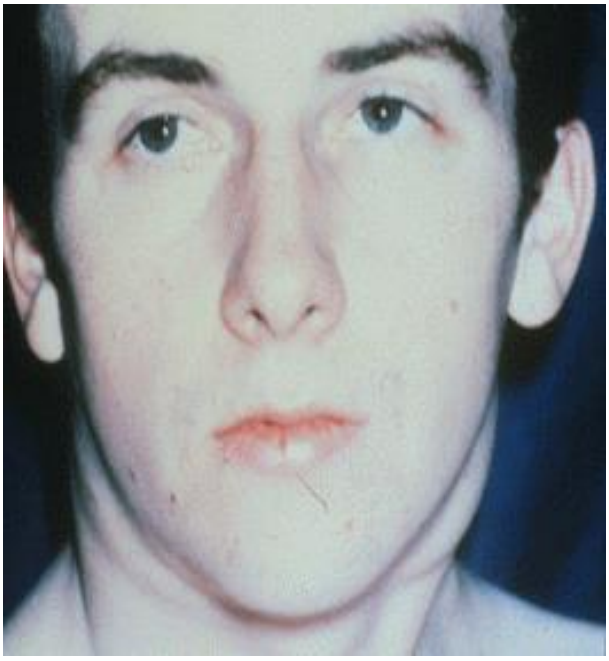


Figure 1Cervical lymphadenopathy

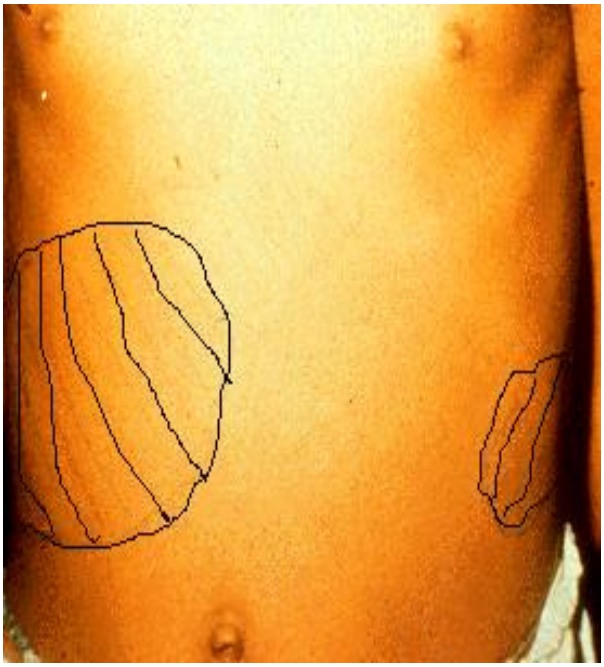
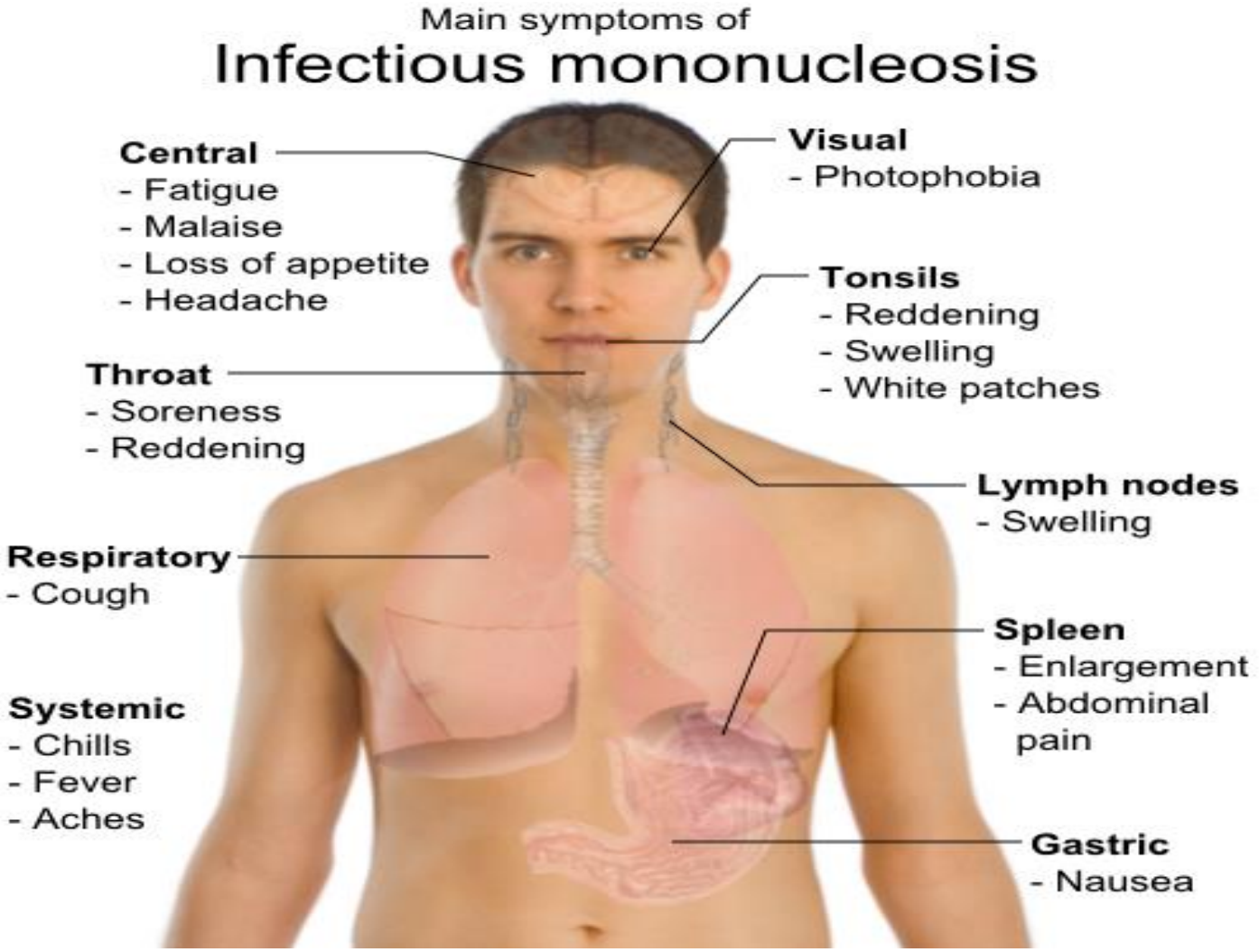
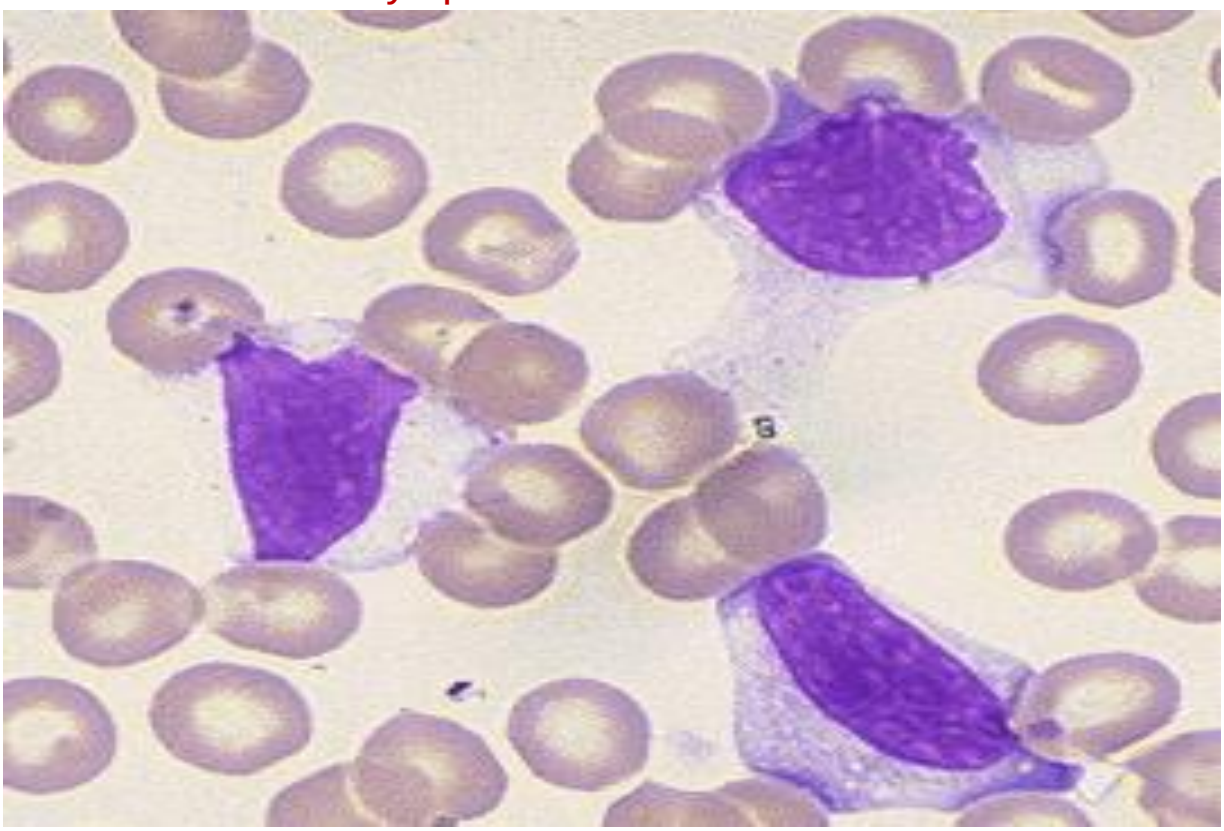


Figure 2Hepatosplenomegaly



Infectious Mononucleosis: Investigation

- The 3 classic criteria for laboratory confirmation
  1- lymphocytosis
  2- the presence of at least 10% atypical lymphocytes on peripheral smear
  3- a positive serologic test for Epstein-Barr virus (EBV).
- Complete blood count
  - 40-70%, Leukocytosis (WBC 10,000-20,000 cells per cm3)
  - By the second week of illness, approximately 10% have a WBC count > 25,000 per cm3.
  - 80-90% of patients have lymphocytosis, with greater than 50% lymphocytes. Lymphocytosis is greatest during 2-3 weeks of illness and lasts for 2-6 weeks.
  - 20-40% of the lymphocytes: atypical lymphocytes > 10%.
  - Mild thrombocytopenia



atypical lymphocytes: Downey types

- Liver function tests
  - 80-100% of patients: elevated LFT
  - Alkaline phosphatase, AST and bilirubin, GGT are elevated.
  - 95% of patients: elevated LDH
  - most liver function test results are normal by 3 months.
- EBV serology
  - EAs (early antigens): early in the lytic cycle
  - VCA (Viral capsid antigen) and membrane antigens: late in the lytic cycle
  - EBNA (Epstein-Barr nuclear antigen): latent infection
  - Antibodies to membrane antigens: usually are not measured
- Time course of antibody production
  - EA is rising at symptom onset: rise for 3-4 weeks, then quickly decline to undetectable levels by 3-4 months, although low levels may be detected intermittently for years.
  - VCA-IgM usually is measurable at symptom onset, peaks at 2-3 weeks, then declines and unmeasurable by 3-4 months.
  - VCA-IgG rises shortly after symptom onset, peaks at 2-3 months, then drops slightly but persists for life.
  - EBNA: convalescence and remain present for life.

IM Treatment

Medical Care:

- self-limited illness: not require specific therapy.
- Inpatient therapy of medical and surgical complications may be required.
- Acyclovir (10 mg/kg/dose IV q8h for 7-10 d)
  - inhibit viral shedding from the oropharynx
  - clinical course is not significantly
- IVIG (400 mg/kg/d IV for 2-5 d)
- Short-course corticosteroids
  - prednisolone (1 mg/kg/d, max 60 mg/d for 7 d and tapered over another 7 d)
  - Marked tonsillar inflammation with impending airway obstruction
  - Massive splenomegaly

  - Myocarditis
  - Hemolytic anemia
  - Hemophagocytic syndrome
  - Seizure and meningitis

Surgical Care:

- Splenic rupture.

Activity:

- depends on severity of the patient's symptoms.
- Extreme fatigue: bed rest for 1-2 weeks.
- Malaise may persist for 2-3 months.
- Patients should not participate in contact sports or heavy lifting for at least 2-3 weeks
- some authors recommend avoiding activities that may cause splenic trauma for 2 months.

IM: Complications

- Hepatitis: > 90% of patients
- Platelet count: approximately 1 week after symptom onset (100,000-140,000/cm3.), then gradually improves over the next 3-4 weeks. Mild thrombocytopenia occurs in approximately 50% of patients with infectious mononucleosis.
- Hemolytic anemia
  - 0.5-3%, associated with cold-reactive antibodies, mild and is most significant during the second and third weeks of symptoms.
- Upper airway obstruction
  - 0.1-1%, due to hypertrophy of tonsils and other lymph nodes of Waldeyer ring
  - treatment with corticosteroids may be beneficial
- **Splenic rupture: 0.1-0.2%**
  - Spontaneous or history of some antecedent trauma.
  - occur during the second and third weeks.
  - mild-to-severe abdominal pain below the left costal margin, sometimes with radiation to the left shoulder and supraclavicular area.
  - Massive bleeding: Shock

- Hematologic complications
  - Hemophagocytic syndrome.
  - Immune thrombocytopenic purpura occurs and may evolve to aplastic anemia.
  - accelerate hemolytic anemia in congenital spherocytosis or hereditary elliptocytosis.
  - Disseminated intravascular coagulation associated with hepatic necrosis has occurred.
- Neurologic complications: < 1%
  - during the first 2 weeks.
  - aseptic meningitis, acute viral encephalitis, coma, meningitis, and meningoencephalopathy.
  - Hypoglossal nerve palsy, Bell palsy, hearing loss, brachial plexus neuropathy, multiple cranial nerve palsies, Guillain-Barré syndrome, autonomic neuropathy, gastrointestinal dysfunction secondary to selective cholinergic dysautonomia, acute cerebellar ataxia, transverse myelitis.
- **Cardiac and pulmonary complications**
  - rare
  - chronic interstitial pneumonitis.
  - myocarditis and pericarditis.
- Autoimmune complications
  - Autoimmune diseases and Reye syndrome have been associated with EBV infection.
  - Renal disorders: immune deposit nephritis, renal failure, paroxysmal nocturnal hemoglobinuria

IM: Prognosis

- Immunocompetent: full recovery in several months.
- The common hematologic and hepatic complications resolve in 2-3 months.
- Neurologic complications
  - Children: resolve quickly
  - Adults: neurological deficits
- All individuals develop latent infection

Prevention

- Isolation is not required: low transmission.
- Avoid contact with saliva.
- Avoid kissing when in acute phase.
- Maintain clean conditions: avoid sharing toys among children in day care.
- Vaccine development is proceeding, although the role of a vaccine is unclear.