A synonym of infectious mononucleosis is the "kissing disease". This term contains also the main method of transmission of Pfeiffer's glandular fever: the kissing. Nearly all people will get infected with the responsible Epstein-Barr virus in the course of their lives. Read the following article for the pathogenesis, symptomatology, diagnosis, and treatment of infectious mononucleosis.
Infectious mononucleosis is a viral infectious disease caused by the pathogen Epstein-Barr virus (EBV) and it is associated especially with fever, angina, pharyngitis, and lymphadenopathy. EBV belongs to the group of human herpes viruses.

Description and synonyms: Infectious mononucleosis (Mononucleosis Infectiosa), Pfeiffer’s disease, Pfeiffer’s glandular fever, mono, “kissing disease.”

Epidemiology of Infectious Mononucleosis

> 95% of people worldwide will be infected with EBV during their lifetime.

Infectious mononucleosis was first described in 1920. It occurs more frequently in spring and autumn. Above all, children and adolescents aged 15 – 19 years are affected. EBV seroprevalence is dependent on age, socioeconomic status, ethnicity, and gender.

In the United States, it is a common cause of viral pharyngitis, especially among young adults.

Note: People who are over 30 years old are almost 100% infected with the Epstein-Barr virus!

Etiology and Pathogenesis of Infectious Mononucleosis

Pathogen of infectious mononucleosis

The Epstein-Barr virus belongs to the human herpesviruses (HHV): HHV 4. The human pathogenic enveloped double-stranded DNA virus was first discovered in 1964 from M. Epstein and Y. Barr from the B lymphocytes of a patient with Burkitt lymphoma.

EBV has an exceptionally high species specificity: it replicates almost exclusively in human epithelial cells of the oropharynx and in B lymphocytes.

Transmission of Pfeiffer’s glandular fever

The disease is mainly transmitted via contact with body secretions primarily oropharyngeal secretions. Other common methods of transmission include:

- Droplet Infection
- Smear infection especially in children by parents, playmates etc.
- Contact infection, especially in adolescents by infected saliva during kissing ("kissing disease")
- NO vertical transmission during pregnancy!
**Note:** There is rarely a transmission of EBV in blood transfusions or transplants. The virus spreads throughout the body from the mouth and infects **CD-21-positive epithelia** in nasopharyngeal space and B lymphocytes that infiltrate tissues. There is an immortalization of the B lymphocytes and a strong increase of EBV. In primary infection, only a small number of viral proteins are likely to be expressed. This results in the initially less pronounced immune response and the lack of clinical symptoms.

An insufficient immune situation, the immune system can destroy the affected B lymphocytes. However, there is never a complete elimination of all viruses, resulting in life-long virus persistence.

**Incubation period of Pfeiffer’s glandular fever**

The incubation period is 10 - 14 days for adolescents and approximately 50 days for adults.

**Symptoms and Clinical Signs of Infectious Mononucleosis**

The prodromal stage is usually asymptomatic, especially in children < 10 years.

**Symptoms of acute mononucleosis**

Typical symptoms of symptomatic Mononucleosis are the following:

**Classic triad:**
Fever

- Tonsillitis
- Cervical lymphadenopathy

**Further symptoms:**

- **Headaches**, pharyngula, limb pain.
- Tonsillitis (similar to Diphtheria) with dirty gray membranes that do not spread locally.
- Typical petechiae at the transition from hard to soft palate.
- Putrefactive Foetor ex-ore.
- Hepatosplenomegaly with jaundice.
- Generalized lymph node swelling (weakly painful, strong, mobile).

**Process:** very long convalescence period (partly for weeks) with weakness and fatigue.

**Note:** The younger the patient (<10 years), the milder the symptoms are. The older the patient (>30 years), the more a part of the classical symptoms is missing.
Hoagland Syndrome

In Hoagland Syndrome, there is a maximum manifestation of infectious mononucleosis. Patients suffer from impaired nasal breathing, periorbital edema, and swollen upper eyelids.

Symptoms of chronic mononucleosis

Persistent viral replication can rarely lead to chronic mononucleosis. Affected patients suffer from fever, fatigue, weight loss, lymphadenopathy, cytopenia, interstitial pneumonia, and hepatitis. Lymphomas with very high lethality also occur.

Case Study

A case of infectious mononucleosis in a medical exam could look like this:

A 19-year-old man is hospitalized because he got sick one week before with malaise and “light” dizziness. One day later, a sudden deterioration with fever up to 40 °C, strong tension headache, dizziness, nausea, and a single vomiting episode occurred. In the further course, the patient complained of a sore throat and discomfort when swallowing, especially of solid food. The doctor ordered an antipyretic drug, as well as Cefuroxime. As there was no improvement in symptoms, he was admitted to the hospital.
Complications of Infectious Mononucleosis

Rare severe Pfeiffer’s glandular fever progression

Severe courses of infectious mononucleosis occur rarely, but they are possible. In addition to the occurrence of autoimmune hemolytic anemia and Thrombocytopenia, the involvement of internal organs can occur, among others, Hepatitis, Myocarditis, Nephritis, interstitial Pneumonia and lymphocytic Meningoencephalitis.

Distinctive splenomegaly can lead to a ruptured spleen. Other complications are Guillain-Barré Syndrome and Portillo’s Syndrome.

Purtilo’s Syndrome

Purtilo’s Syndrome is an X-linked recessive inheritance disorder of the immune response against EBV. No antibodies against antigens of EBV can be formed by the immune deficiency. The result is the self-destruction of the immune system, which can lead to fatal progression (hepatitis, organ infiltration by cytotoxic lymphocytes, hemophagocytic syndrome).

EBV-associated tumors

- Nasopharyngeal carcinoma
- Hodgkin’s disease
- Burkitt’s lymphoma
- B-cell lymphoproliferative disorder

Diagnosis of Infectious Mononucleosis

Physical examination of Pfeiffer’s glandular fever

Infectious mononucleosis is accompanied by enlarged lymph nodes (cervical, axillary and inguinal). Some patients show hepatosplenomegaly. Characteristic are the crimson, swollen tonsils with the typical dirty gray membranes.
Pfeiffer’s glandular fever in lab

**Significant lab results for infectious mononucleosis are:**

- Absolute and relative leukocytosis (> 4000/ml and > 50% of leukocytes) with > 10% atypical large T-cells (*Pfeiffer cells*, fibrocytes)
- Mild anemia, neutropenia, and thrombocytopenia
- BSR ↑
- CRP ↑
- Transaminases ↑

**Note:** Pfeiffer’s gland cells are characterized by a basophilic vacuole in the cytoplasm and eccentrically localized, subdivided nucleus.

Tests for the detection of Pfeiffer’s glandular fever

The gold standard for infectious mononucleosis is ELISA. The protection is achieved by the detection of virus-specific IgM antibodies (against the viral capsid antigen). Infection takes place by the detection of EBNA IgG antibodies.

**Paul Bunnell Test**

Low specificity and sensitivity. It characterizes the mononucleosis rapid test hardly plays a role in current diagnostics.

Histology of Pfeiffer’s glandular fever

Typical in infectious mononucleosis is the picture of polymorphic hyperplasia of the pulp: propagation in lymph nodes and fast-growth of blast cells/necrosis are presented in the histological sample.

Differential diagnoses of Infectious Mononucleosis

**Pfeiffer’s glandular fever – pure clinical delimitation difficult**

**Note:** Clinically, no distinction is made between an acute EBV, a CMV, and an HIV infection!

- Acute CMV, HIV, group A streptococcus, Toxoplasma infections.
- Rare HHV-6, HHV-7, Parvovirus B19, Bartonella infections.
- Viral Rhino-, corona-, adenoviruses infections: they frequently occur on a seasonal basis and they are accompanied by intensified cold symptoms.
- Parainfluenza viruses: sudden myalgia/arthralgia with fever in a mild case of tonsillitis.
- Diphtheria.
- Acute necrotizing ulcerative gingivitis: often development of necrosis and dirty-gray pseudomembrane.
- Listeriosis: listeria infection may be considered in the case of negative EBV results.
Treatment of Infectious Mononucleosis

Symptomatic treatment of Pfeiffer’s glandular fever

There is currently no specific antiviral therapy available. The **symptomatic treatment** includes physical preservation and antipyretics and analgesics like Paracetamol and/or non-steroidal antirheumatics and volume loading. The administration of penicillin and aminopenicillins can trigger exanthema formation.

**CAVE:** No antiviral medication, such as acyclovir and valaciclovir, should be used in patients with adequate immune function.

Prognosis of Infectious Mononucleosis

Best course of Pfeiffer’s glandular fever

The prognosis of infectious mononucleosis is, in normal cases, good. In patients with cellular immunodeficiencies and post-transplant patients, more severe courses may occur. Chronic infections are extremely rare.

Review Questions

The correct answers can be found below the references.

1. **Differential diagnosis of infectious mononucleosis, which is clinically very similar, must be excluded. Which of these pathogens is the most probable one?**

   A. Human Immunodeficiency Virus (HIV)
   B. Epstein-Barr virus
   C. Respiratory Syncytial Virus (RSV)
   D. Coxsackievirus
2. An 11-year-old pupil presents with fever, Tonsillitis, and cervical lymphadenopathy. What is the diagnosis?

A. Rubella  
B. Infectious mononucleosis  
C. Scarlet fever  
D. Parotitis  
E. Measles

3. A definite constellation of lab results is typical in the diagnosis of Pfeiffer’s glandular fever. Which of the following results is the most improbable one?

A. BSR ↑  
B. CRP ↑  
C. Transaminases ↑  
D. Leucopenia  
E. Thrombocytopenia

References


**Correct answers**: 1E, 2B, 3D

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