



Infectious Mononucleosis

(EBV infection, Pfeiffer's glandular fever)

Epstein-Barr virus-Transmission and persistence in B-cells

Some of the EB-viruses remain latent in the B-lymphocytes („memory cells“) after an infection. In an intact immune system, they are controlled for life by T-cells. A reactivation can, for example, occur in the event of immunosuppression.

The Epstein-Barr virus is transmitted via the saliva of infected persons, which has also given the infection the name „kissing disease.“ The infection is common in children, adolescents and young adults.

The virus is very common—approx. 95% of people 30 years of age and above are infected with EBV. Since the disease is often asymptomatic, many people do not even know that they have gone through an infection. The infection can be verified by serology by the presence of IgG-EBNA antibodies.

Differentiation between monocytes / reactively altered lymphocytes

Monocytes have a homogeneous gray-blue („dove gray“) cytoplasm. It may be slightly darker basophilic if it is associated to an erythrocyte. However, this basophilia is limited to a fine border zone. The monocyte plasma often contains vacuoles.

In contrast, reactive lymphocytes show an increasing cytoplasmic basophilia, which is specifically notable around the borders, but always continues in the direction of the nucleus, where it becomes increasingly brighter. This „color progression“ toward the nucleus is typical for reactive lymphocytes.

Introduction

Infectious mononucleosis (also „Pfeiffer's disease“) is caused by infection with the Epstein-Barr virus (EBV). Approx. 95% of adults have gone through EBV infection. The course of a large number of EBV infections is asymptomatic. In clinically manifested infections, patients suffer from headache, fatigue, fever, lymph node swelling, pharyngitis (inflammation of the throat), splenomegaly (enlargement of the spleen) and minor hepatomegaly (enlargement of the liver), among other symptoms. The hematological finding reveals lymphocytosis with usually increased WBC numbers and reactively altered lymphocytes. The distinction of these cells from neoplastic lymphocytes in malignant lymphoproliferative diseases can sometimes be difficult by morphology alone. The definitive diagnosis is made by serological detection of antibodies against EBV, or by molecular genetic analyses via detection of the viral DNA by PCR. The current proficiency testing survey samples are from a 21-year-old patient with EBV infection.

Pathophysiology

The Epstein-Barr virus (EBV) belongs to the group of herpes viruses. It is spread by saliva and infects epithelial cells of the throat area as well as B-lymphocytes. The infection triggers a cytotoxic T-cell response. With the influx of the virus, the infected B-lymphocytes transform into lymphoblastoid cells, which produce heterophilic antibodies. The reactively altered lymphocytes typically found in the blood picture with EBV infections are activated T-lymphocytes and NK cells (natural killer cells). In addition, a small number of altered cells with blast-like aspects are found which are usually B-lymphocytes.

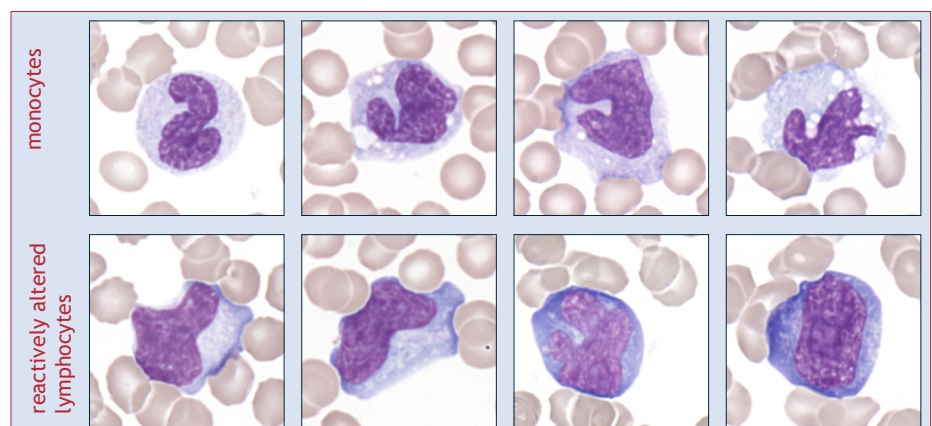
Laboratory results

Findings	Incidence	Comment
Lymphocytosis abs./rel.	99 %	> 60% lymphocytes (usually 6-18 G/l)
atypical lymphocytes	99 %	reactive changes
Neutropenia	60-80%	promotes bacterial super-infections
Thrombocytopenia, minor	25-50%	
Anemia, severe	selten	autoimmune hemolytic (auto-antibodies)
EBV antibodies in the serum	100%	VCA-IgM, VCA-IgG and IgG-EBNA (appear in this order over the course of the infection)
Heterophilic serum IgM-ab	80-100%	mononucleosis Quick Test („Mono spot“)
EBV DNA (PCR)	100%	
abnormal liver values	80-100%	ALT, AST
Cold agglutinins	10-50%	
Hyperbilirubinaemia	30-50%	

* VCA = Virus capsid Antigen (viral envelope), EBNA= nuclear antigen

Source: «Diagnostische Hämatologie» H.Huber, H.Löffler, D. Pastner

Differentiation between monocytes / reactively altered lymphocytes





Variability of reactively altered lymphocytes

The morphological variability is large within the lymphocyte population („colorful picture“). It can vary greatly from patient to patient as well as within the various stages of infection.

The size variability of the cells is impressive. In addition to lymphocytes with only minor enlargement of up to approx. 15 µm; very large cells with a cell diameter of up to 25 µm can also be found.

While reactively altered lymphocytes with a cell diameter of up to approx. 20 µm can be found in various viral diseases (rubella, measles, viral hepatitis), the highly enlarged elements with a cell diameter of >20 µm are typically found in EBV (Epstein-Barr virus), CMV (cytomegalovirus), primary HIV infection and toxoplasmosis.

About

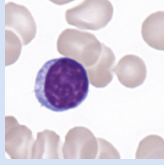
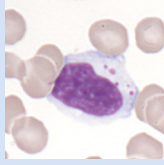
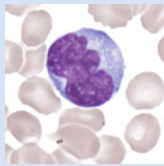
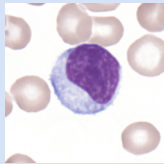
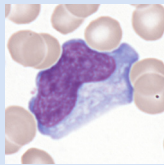
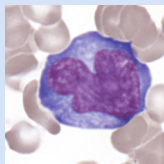
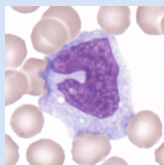
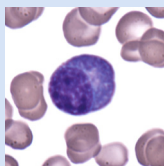
Autor Annette Steiger
Photos Dr. Roman Fried

Advisory
K.Schreiber, Dr. J. Goede, Klinik für
Hämatologie, Universitätsspital Zürich

Lymphocyte morphology

The morphology of reactive changed lymphocytes lies between lymphocytes, plasma cells and monocytes. The cells are of varying size (8 -25µm) and show abnormalities with respect to the nucleus shape and structure and variations in the amount of cytoplasm and staining (polymorphic with respect to size and nucleus).

The number of names used for these cells is also large and varies from lab to lab (reactive lymphocytes, altered lymphatic forms, virocytes, Pfeiffer's cells, lymphomonocytes, transformed lymphocytes).

Cell	size	nucleus	cytoplasm
Normal lymphocyte 	8-10 µm	round, chromatin dense-lumpy	narrow, basophilic
LGL - large granular lymphocyte (NK cell) 	10-12 µm	slightly oval, chromatin dense	medium width, brightly basophilic with coarse azurophilic granulation
Reactively altered lymphocytes    	10-15 µm	Indented or irregular, chromatin dense	medium width, slight outer edge basophilia, brighter toward the nucleus.
	10-15 µm	Round to minimally indented, eccentrically located, chromatin dense	medium broad, slightly basophilic edge zone, brighter toward the nucleus.
	15-20 µm	indented, irregularly relaxed chromatin, possible nucleoli	medium width, circumferential borders possibly adjacent erythrocytes, distinct border basophilia with perinuclear brightening
	20-25 µm	irregular, notched, chromatin fine, often one to several nucleoli	wide, circumferential borders, possible adjacent erythrocytes, distinct wide border basophilia with perinuclear brightening
Monocyte 	12-20 µm	elongated, bean-shaped, indented, chromatin finely structured, „sponge-like“, no nucleoli	medium width, gray-basophilic, often with vacuoles, fine azurophilic granules.
Plasma cell 	8-14 µm	eccentrically located, round, coarse-lumpy chromatin	dark basophilic with prominent perinuclear halo. No nucleoli.