



### Lymphocytes - subtypes

Based on different surface antigen patterns, lymphocytes are associated to different developmental stages.

- B cell lineage
- T cell lineage
- NK cell lineage

Lymphocytes cannot be unequivocally assigned to individual lineages by morphology.

A precise designation is possible only by detecting specific surface markers expressed on the lymphocyte (immunophenotyping).

Immature lymphoid cells that are found in the peripheral blood morphologically appear in the form of blasts.

### Glossary

#### CD8 receptor

Membrane protein that allows T cells to bind to the MHC-1 complex on the target cell.

#### Proliferation

Growth and reproduction of cells

#### neoplastic

New formation (here: of malignant cells)

#### naive cells

Cells, which have not previously encountered antigen

#### MHC molecules

Major histocompatibility complex

Surface antigens to identify the body's own cells.

#### Lymphatic organs

##### primary:

Thymus and bone marrow (bursa-equivalent)

##### secondary:

Lymphoid follicles, Peyer's patches, tonsils, spleen, lymph nodes, appendix.

#### Immunophenotyping

Laboratory method used to detect antigens expressed on the cell surface.

### Introduction

Lymphocytes play an important role in immune defense against foreign substances, in particular against infectious agents and malignant cells (e.g., tumor cells) in the organism. In the context of (mostly) viral infections, reactive lymphocytes appear with a morphology that differs from that of typical lymphocytes. Various types of malignant lympho-proliferative disorders such as Hodgkin's lymphoma and non-Hodgkin's lymphomas of B, T and natural killer cells (NK cells) also exist, which can lead to proliferation of morphologically atypical lymphoid cells.

Our current survey specimen 2014-03 is derived from a 44-year-old man with mantle cell lymphoma.

### Development and function

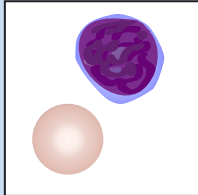
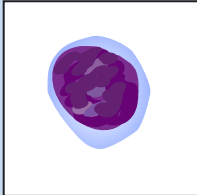
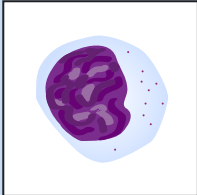
Lymphocytes develop from lymphoid stem cells in the bone marrow from where they enter the blood and lymph vessels. Approximately 85% of lymphocytes in the thymus are dedicated to their future role in cellular defense (T-cells), 15% enter directly into the lymphoid tissue where they differentiate further and may proliferate (B-cells).

**T-cells** are responsible for cellular immunity. They are mobilized when they encounter cells presenting parts of a foreign antigen on endogenous MHC molecules. The influence of cytokines causes production of more T-cells:

- **T-helper cells** - attract other immune cells.
- **Cytotoxic T-cells** - render virus-infected cells harmless.
- **Regulatory T cells** - prevent hyper-reactivity towards the body's own cells.

**Naive B cells** are B-cells that have not yet encountered antigen; they recognize foreign antigens via their receptors. They often require co-stimulation by T helper cells. They subsequently migrate into the germinal centers of lymph nodes and the spleen where they proliferate and differentiate into antibody-producing plasma cells. Some of these plasma cells turn back into B-lymphocytes and are persist as memory cells in lymphoid tissues.

### Morphology of typical lymphocytes

Typical lymphocyte	Typical lymphocyte	LGL cell
		
<p><b>Size</b> Cell diameter approx. 10 µm Nucleus diameter approx 7 µm</p> <p><b>Nucleus</b> round to slightly oval</p> <p><b>Nuclear chromatin</b> dense to coarse, no nucleoli</p> <p><b>Cytoplasm</b> narrow, light-basophilic with smooth border</p>	<p>Occasionally, because of a slightly increased cytoplasmic portion, lymphocytes may be found that appear somewhat larger.</p> <p>Their cytoplasm is also homogeneously light-basophilic up to the borders and nongranular. The nuclear chromatin is dense and has no nucleoli.</p>	<p>Large granular lymphocyte (LGL) cell</p> <p>These are cytotoxic T cells or natural killer cells (NK cells) that are CD8-positive.</p> <p>Somewhat larger than typical lymphocytes, cytoplasm light-basophilic and broad, some granularity, irregularly distributed azurophilic granules.</p>

Lymphocytes with the above-described morphology constitute approximately 50% of circulating leukocytes in healthy individuals. Lymphocytes that cannot be assigned to one of these typical forms are to be considered **atypical**.

These atypical forms include a wide range of morphological variations of cell size, chromatin, cytoplasm color etc. They arise either in response to viral infection or as **neoplasms** in the context of malignant lympho-proliferative disorders (non-Hodgkin's lymphoma).

Based on purely morphological aspects, reactive and neoplastic origins cannot always be clearly differentiated. Thus, complementary laboratory analyzes are often required such as infection serology or PCR analysis with suspected viral infections and/or determination of antigen expression on the surface of lymphocytes by immunophenotyping.



**Classification of different morphological forms of lymphocytes**

In future, we will use the following nomenclature, which several European countries are in agreement with [1,2].

The forms of lymphocytes normally found in the blood of healthy individuals are referred to as «typical lymphocytes.»

Cells that are morphologically indistinguishable from the typical lymphocytes, such as CLL lymphocytes or LGL cells in LGL leukemia, are also included in the group of «typical lymphocytes.» If more than 10% LGL cells appear in the smear or if there is suspicion of CLL, it must be pointed out in the comments..

Lymphocytes with deviating morphology are referred to as «atypical lymphocytes.»

Lymphocytes that appear in viral infections are referred to as «atypical lymphocytes, presumably reactive.»

Lymphocytes that appear in neoplastic processes are referred to as «atypical lymphocytes, presumably neoplastic.» In the commentary, the cells are named when possible (e.g., hairy cells). If this is not possible, the cell morphology is described.

1. Zini, G et al. A European consensus report on blood cell identification. Br J Haematol 2010;151:359-64.
2. Baurmann, H. Lymphozytenmorphologie im Blutausstrich. J Lab Med 2011;35(5):261-270.

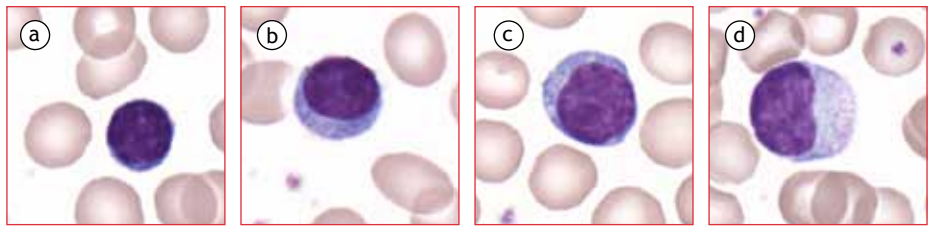
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**Typical lymphocytes**



a) typical lymphocyte, small, dense, little cytoplasm (MQ 2014-2 H3A)  
b+c) typical lymphocytes, small, dense, wide cytoplasm border without granulation (MQ 2014-2 H3A)  
d) typical lymphocyte, LGL cell, cytoplasm broad and bright with azurophilic granules

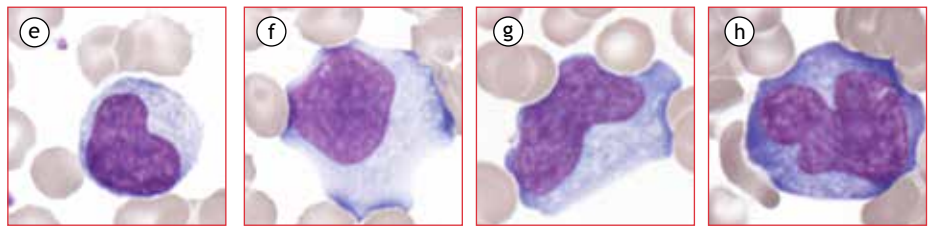
**Atypical lymphocytes**

The appearance of «atypical lymphocytes» is usually accompanied by an overall increase of lymphocytes relative to the total leukocytes (> 50%).

Morphologically, reactive «atypical lymphocytes» present a rather «colorful picture» with various aspects differing from typical lymphocytes.

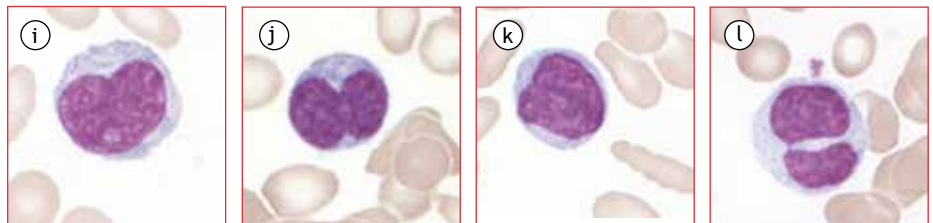
In contrast, because of their clonality, neoplastic «atypical lymphocytes» in clinical pictures often present a uniform, monotonous picture of morphological deviations.

**Atypical lymphocytes, presumably reactive**

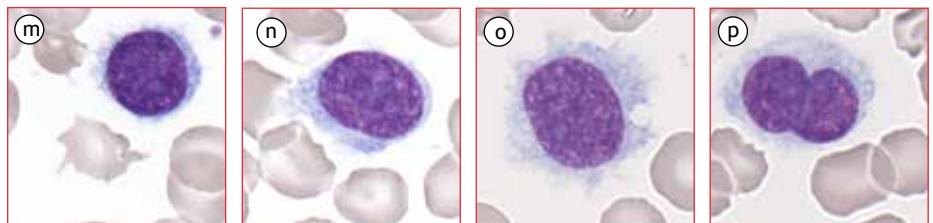


e-h) Reactive lymphocytes in EBV infection (MQ 2012-2 H3B)

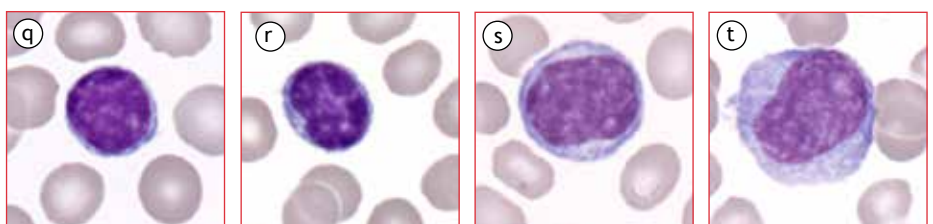
**Atypical lymphocytes, presumably neoplastic**



i-l) Atypical lymphocytes in mantle cell lymphoma (MQ 2014-3 H3B)



m-p) Atypical lymphocytes in hairy cell leukemia (MQ 2013-2 H3B)



q+r) Typical lymphocytes in CLL (MQ 2010-1 H3B)  
s+t) Atypical lymphocytes presumably neoplastic: pro-lymphocytes in CLL (MQ 2010-1 H3B)