

Chapter 7 Qualitative abnormalities in lymphoid cells– Reactive lymphocytes

Mindray Morphology Corner / Series Course-II WBC

Accurate Recognition of Lymphocyte Morphologic Changes to Enhance Benign-Malignant Differentiation.

Lymphocytes are important immune cells. In response to various antigenic stimuli, they may undergo morphological changes and appear in increased numbers in the peripheral blood. Such immune stimulation can occur in inflammatory and infectious diseases, particularly viral infections, as well as in neoplastic disorders such as leukemia and lymphoma.

It is recommended that **reactive lymphocyte** is used to describe lymphocytes with a **benign aetiology** and **abnormal lymphocyte** with an accompanying description of the cells is used to describe lymphocytes with a suspected **malignant or clonal aetiology**.

Reactive lymphocytes exhibit morphological polymorphism, heterogeneity, and reversibility. Following removal of the stimulating factor, they gradually return to normal morphology and do not show clonal proliferative features. Their identification is a key criterion for differentiating benign and malignant lymphoid lesions in clinical blood morphology.

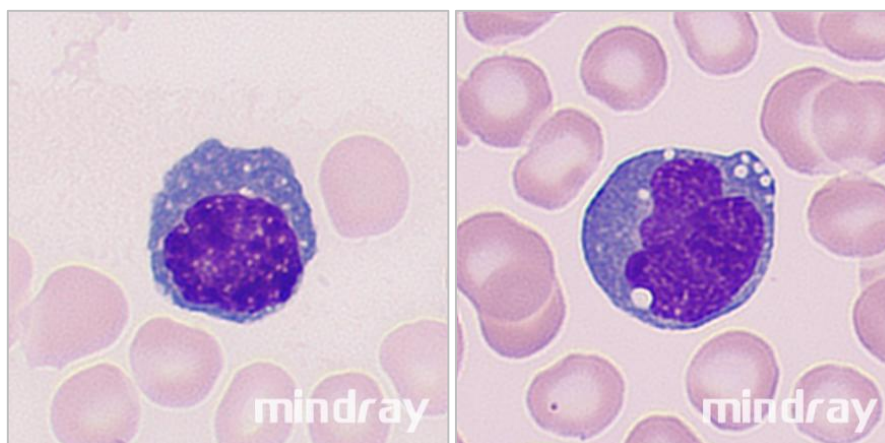
I. Morphological classification of reactive lymphocytes

The clinical morphological examination uses the Downey's three typing criteria, which are based on cell size, cytoplasm, nucleus, and chromatin characteristics. Each type has typical and highly recognizable morphological features, and is the core basis for identifying reactive lymphocytes in peripheral blood smears.

1. Type I Reactive Lymphocyte (Plasmacytoid Type)

This type is the most common, often seen in the early stages of viral infection, and is the basic form of activated lymphocytes.

- **Size:** Medium-sized, slightly larger than normal lymphocytes; round to oval in shape.
- **Cytoplasm:** Abundant, **deep blue cytoplasm** with numerous variably sized **vacuoles**, giving a foamy appearance; **no obvious granules**.
- **Nucleus:** Variable nuclear shape (round, oval, kidney-shaped, or irregular) with coarse clumped chromatin; **Unclear or absent nucleoli**.
- **Key feature:** Morphologically resembling plasma cells, nuclear maturation, cytoplasmic activation with vacuoles, overall mature activation morphology.



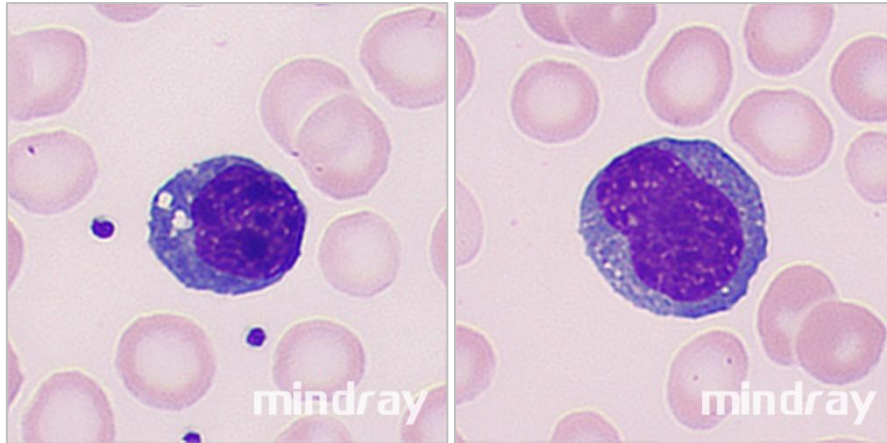


Figure 1

2. Type II Reactive Lymphocyte (Monocytoid Type)

The clinical detection rate is high, and the morphology is easily confused with monocytes, which is the focus of morphological differentiation

- **Size:** The cell size is significantly enlarged compared to type I cells, with an irregular appearance resembling monocytes.
- **Cytoplasm:** Rich cytoplasm, light blue or blue, transparent, uneven coloring, darker blue at the edges, skirt like, may have a few azurophilic particles, generally no vacuoles.
- **Nucleus:** The morphology of the cell nucleus is irregular, and the chromatin is sparse and delicate.
- **Key feature:** Irregular nuclear shape, rich cytoplasm with a grayish blue tint, resembling monocytes, may have a few azurophilic particles.

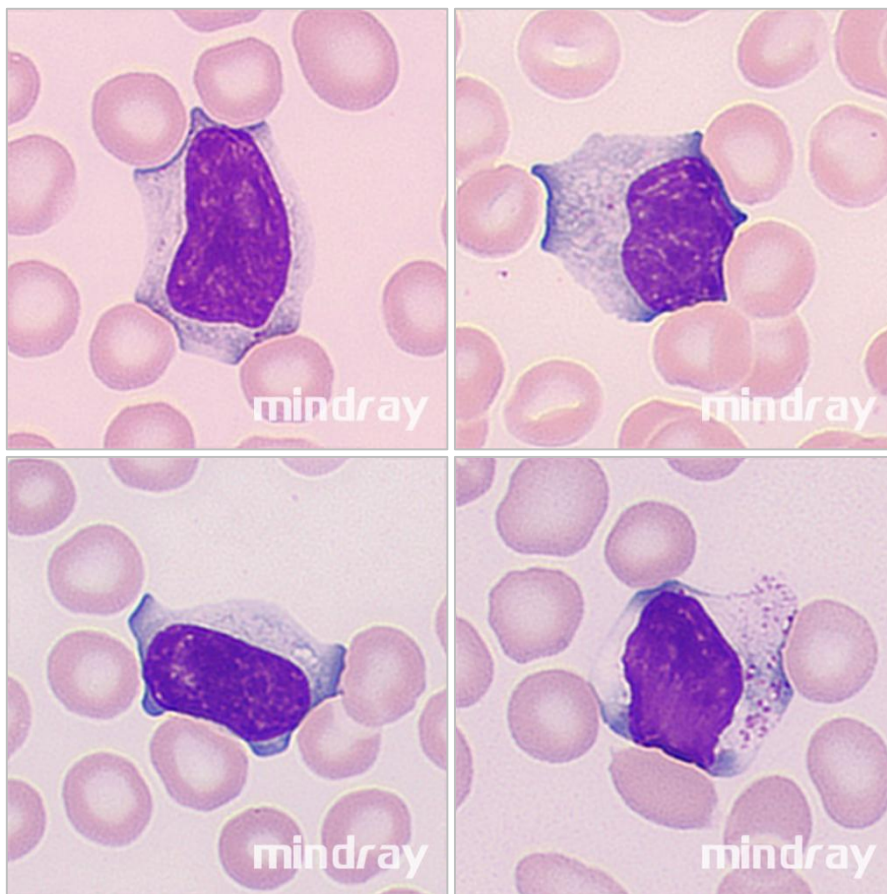


Figure 2

3. Type III Reactive Lymphocyte (Immunoblastic Type)

Commonly seen during peak infection periods and severe immune activation, with a morphology similar to blast cell and immature lymphocytes, it is easily misdiagnosed as malignant lymphocytic leukemia cells, which is a difficult clinical differentiation point.

- **Size:** The cell size significantly increases, making it the largest of the three types in terms of volume.
- **Cytoplasm:** Less cytoplasm, dark blue in color, mostly without particles, occasionally with small vacuoles.
- **Nucleus:** The nucleus is large, round in shape, and the chromatin is finely reticular. Clear nucleoli can be seen, with 1-2 nucleoli.
- **Key feature:** Immature nucleus, visible nucleoli, overall morphology similar to Lymphoblast.

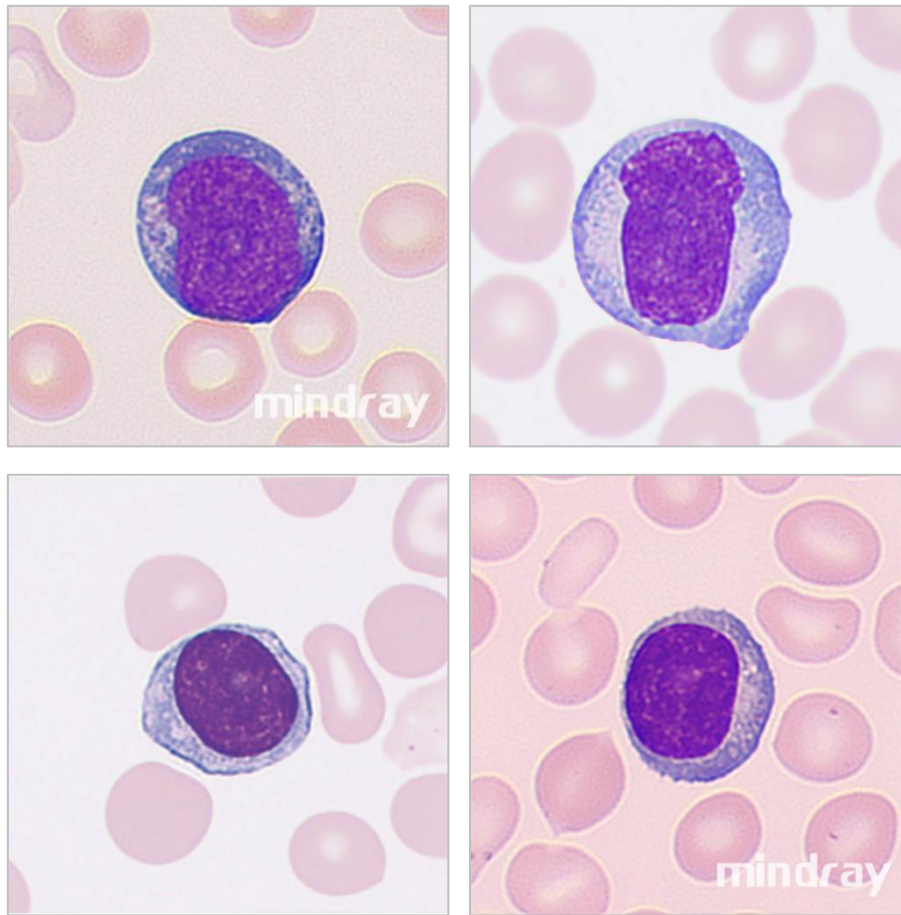


Figure 3

4. Summary

Classification	Key morphological features
Type I	Deep blue cytoplasm with foamy vacuoles; eccentric nucleus, coarse chromatin, no nucleoli
Type II	Large cell, slate-blue cytoplasm with skirt-like margins; few azurophilic granules, no obvious vacuoles
Type III	Fine reticular nuclear chromatin, nucleoli visible; deep blue cytoplasm, similar to Lymphoblast

II. Differentiation between reactive lymphocytes and other cell types

Reactive lymphocytes are a subtype of lymphocytes. Rapid recognition of their morphological changes and differentiation from normal lymphocytes are of great clinical value.

In addition, some reactive lymphocytes exhibit features such as cytoplasmic vacuoles, irregular cell morphology, and prominent nucleoli (Figure 4.1~3). These characteristics may result in morphological similarities to monocytes (Figure 4.4) and blast cells (Figure 4.5), making accurate identification more challenging. Therefore, a clear understanding of their distinguishing morphological features is essential for rapid and reliable differentiation.

The following section summarizes the key morphological characteristics that may assist in their prompt identification.

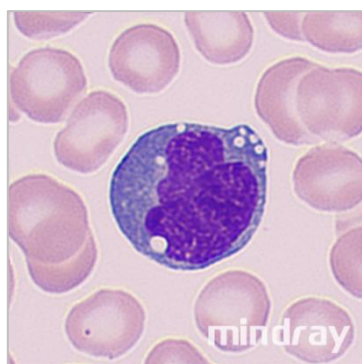


Figure 4.1 (Type I)

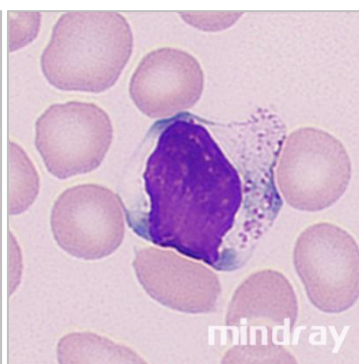


Figure 4.2 (Type II)

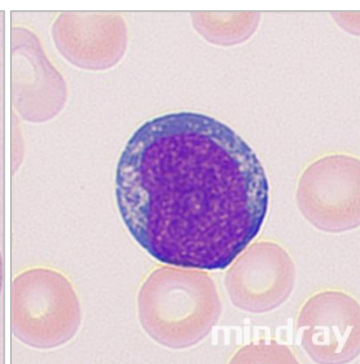


Figure 4.3 (Type III)

Reactive lymphocyte

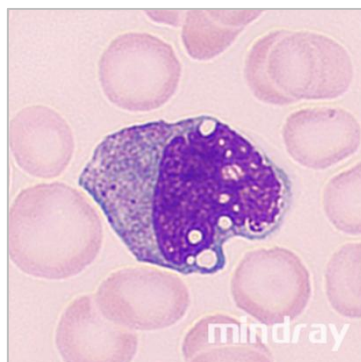


Figure 4.4
Monocyte



Figure 4.5
Blast

Feature	Reactive Lymphocyte	Monocyte	Prolymphocyte/Blast
Cell size	Pleomorphic , marked variation between cells	Relatively large	Relatively uniform (neoplastic)
Nucleus shape	Round/eccentric/slightly irregular; no marked folding	Irregular, folded, twisted, wrinkled nucleus	Round or oval, distinct nuclear membrane, slight indentation; no monocyte-like folds
Chromatin	Coarsely reticulated, moderately loose;	Loosely reticulated, sieve-like pale staining, no large clumps	Fine dusty / finely reticulate, evenly distributed

Feature	Reactive Lymphocyte	Monocyte	Prolymphocyte/Blast
Nucleoli	Absent in type I & II; 1–2 small nucleoli in type III	Usually absent	1 or more prominent, distinct nucleoli
Cytoplasm amount	Moderate to abundant; type I deep blue with foamy vacuoles; type II gray-blue with deep blue skirt-like rim; type III deep blue	Abundant, gray-blue/gray-red, ground-glass (cloudy)	Scant to moderate, basophilic blue
Granules	Few azurophilic granules in type II	Fine dust-like azurophilic granules, evenly distributed	Usually agranular
Vacuoles	Numerous foamy vacuoles in type I; rare vacuoles in type II & III	Scattered fine vacuoles, no large foamy vacuoles	Few or no vacuoles
N/C ratio	Medium to low (abundant cytoplasm)	Low, very abundant cytoplasm	High (scant cytoplasm)

● **Memory tips for confusing pairs**

- **Type II reactive lymphocyte vs Monocyte:** reactive lymphocyte → deep-blue skirt-like cytoplasmic rim; monocyte → uniform gray-blue ground-glass cytoplasm with dust-like granules; monocyte nucleus is more folded.
- **Type III reactive lymphocyte vs Prolymphocyte/blast:** reactive lymphocyte shows cellular pleomorphism; Prolymphocytes are relatively uniform with more prominent nucleoli.

III. Clinical Application Value

An increase in reactive lymphocytes in the blood is a reliable indicator for identifying viral infections, more accurate than merely checking changes in the total lymphocyte count, and is widely used in clinical practice.

First, reactive lymphocytes are valuable indicators of **viral infection**. Infectious mononucleosis, which is most commonly caused by Epstein-Barr virus (EBV), is the classic example. In affected patients, **reactive lymphocytes typically account for more than 10% of peripheral blood leukocytes**, providing important diagnostic clues when interpreted together with clinical manifestations. Besides, other viral infections, such as cytomegalovirus infection, may also lead to varying degrees of reactive lymphocytosis. This feature can help distinguish viral infections from bacterial infections, which are more commonly characterized by neutrophilia. Furthermore, the morphology and proportion of reactive lymphocytes may reflect **the stage and severity of infection**. Type I cells are usually predominant during the early phase of infection, Type III cells become more prominent at the peak of disease, and the cells gradually return to normal morphology during recovery.

Second, when the body is under stress due to autoimmune disorders, drug allergies, vaccination or other conditions, the immune system becomes activated, leading to mild or moderate growth of reactive lymphocytes. This reflects **inflammation and active immune response** in the body.

Most importantly, reactive lymphocytes help **distinguish benign immune reactions from severe malignant lymphoid lesions**. In benign cases, cells have varied shapes and scatter individually without abundant abnormal immature cells; the condition resolves spontaneously

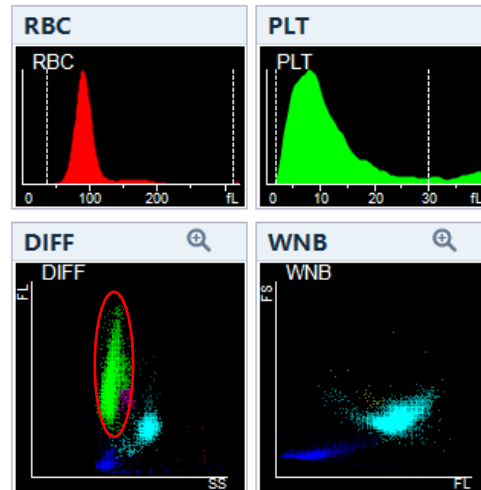
as the body recovers. In contrast, malignant conditions such as leukemia and lymphoma feature uniformly shaped cells with dense clusters of abnormal immature cells and obvious structural defects. They are often accompanied by anemia and disturbed platelet and white blood cell counts. These serious diseases require close attention.

● Clinical Case for Infectious Mononucleosis

1. Case Sharing I

➤ Blood routine screening

Parameter	Results
WBC	H 18.81
Neu#	R 4.21
Lym#	RH 14.45
Mon#	RL 0.11
Eos#	L 0.01
Bas#	0.03
IMG#	R 0.08
Neu%	RL 22.4
Lym%	RH 76.8
Mon%	RL 0.6
Eos%	L 0.0
Bas%	0.2
IMG%	R 0.4
RBC	4.46
HGB	134
HCT	40.4
MCV	90.5
MCH	30.0
MCHC	331
RDW-CV	13.1
RDW-SD	43.7
PLT	160
MPV	10.7
PDW	16.3
PCT	0.172
P-LCC	51
P-LCR	31.6
NRBC#	0.000
NRBC%	0.00



Flag
- Blast?
- Abnormal lymphocytes / Blast?
- Atypical lymphocytes
- Lymphocytosis
- Leukocytosis

🚩 Interpretation:

The hematology results showed an increase in WBC, a significant increase in lymphocyte proportion, and no abnormalities in the RBC and Platelet.

The DIFF scattergram, shows that the Lym cluster extends towards the high fluorescence area, and the analyzer gives an alarm for "Blast? Abnormal lymphocytes / Blast? And atypical lymphocytes".

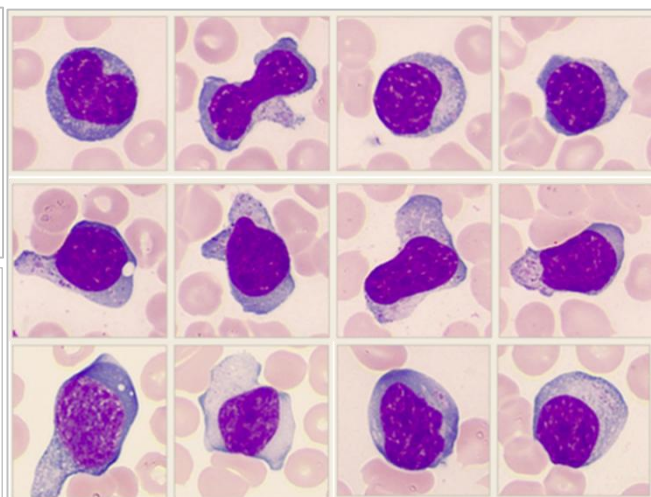
➤ Morphological examination

WBC	Flag	Count	%
Segmented neutrophils	L	23	23.0
Band neutrophils	!	10	10.0
Lymphocytes		33	33.0
Monocytes	L	2	2.0
Basophils		1	1.0
Metamyelocytes		1	1.0
Reactive lymphocytes	!	30	30.0



Peripheral blood cell

morphology: Reactive lymphocytes account for 30%, and no significant abnormalities are observed in other cells.



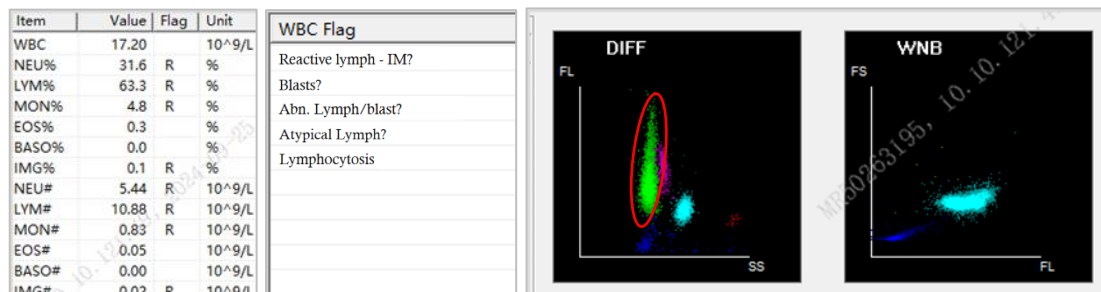
Other tests: Cytomegalovirus: IgM antibody negative (-), Epstein – Barr virus (EBV) IgM, IgG antibody positive (+)

2. Case Sharing II

➤ Blood routine screening

🚦 Background:

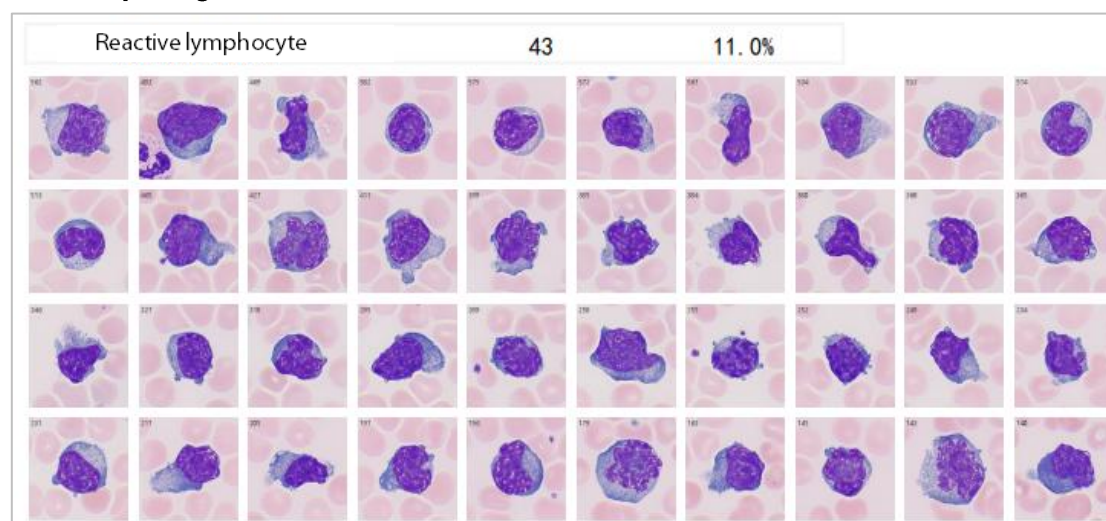
Patient: male, 7 years old, presenting with cough for 5 days, fever for 3 days, and temperature 37.9°C



🚦 Results analysis:

The blood routine examination shows that the lymphocyte proportion increases and the scattergram is abnormal. "Reactive lymph - IM?" message

➤ Morphological examination



🚦 Peripheral blood cell morphology: Reactive lymphocyte: 11%

➤ Subsequent Inspection

Admission, reactive lymphocyte binding test in peripheral blood. Several lymph nodes of large and small fava beans can be palpated on both sides of the neck. The lymph nodes are soft and well-defined without tenderness. The eyelids are slightly puffy. The tonsil is enlarged in the second degree. Secretion can be seen.

🚦 IM suspected? → EBV capsid antigen IgM antibody 173.00U/mL (Acute stage of IM)

Combined with other examinations, the patient is diagnosed with IM.

● Case Review

The patient sought medical attention, and the initial blood routine screening revealed abnormal classification of WBC. The scattergram of lymphocytes and monocytes could not be distinguished, and the lymphocyte count increased, accompanied by abnormal cell alarm/Flag prompts. Therefore, it is necessary to confirm the results through slide microscopy. Microscopic

morphology revealed a large number of reactive lymphocytes, **exceeding 10%**, suspected of **infectious mononucleosis**. Suggest adding virus antibody testing, the result confirms positive EB antibody. **Morphology assists clinical diagnosis, quickly identifies causes, and improves diagnostic and therapeutic efficiency.**

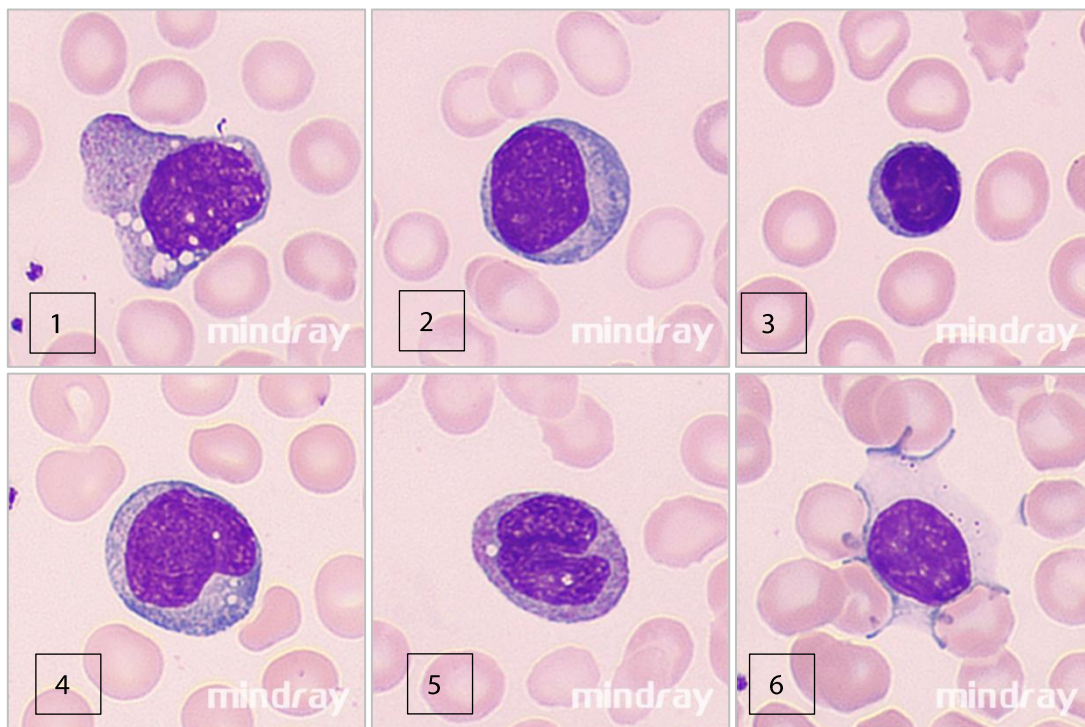
References & Image Sources

References:

1. Palmer L, Briggs C, etc., ICSH recommendations for the standardization of nomenclature and grading of peripheral blood cell morphological features. Int J Lab Hematol. 2015 Jun;37(3):287-303.
2. Bain BJ. *Blood Cells: A Practical Guide*. 6th ed. Wiley-Blackwell; 2021.

Images & Technical Support: Some morphology images in this course are derived from analysis by the **Mindray automated digital morphology analyzer MC-80**.

Practice



[The answers will be at the end of the next chapter]

The answer of last chapter:

- 1.Abnormal promyelocyte, 2.Blast, 3.Abnormal promyelocyte (with Auer rods),
4. Promonocyte, 5.Cup-like blast, 6.Monoblast

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— Coming Next: **Qualitative abnormalities in lymphoid cells—Abnormal lymphocytes—**