

Lymphocyte

SYNONYMS

none

VITAL STATISTICS

size	7 to 15 μm
n:c ratio	5:1 to 2:1
cell shape	round to ovoid
nuclear shape	usually round to oval; occasionally notched or slightly indented
chromatin	diffusely dense or coarse with clumped masses; minimal to absent parachromatin; minimal to absent chromocenters
nucleoli	ranging from not visible to small and indistinct
cytoplasm	scant to moderate; pale blue to moderately basophilic; agranular to few coarse azurophilic granules; small paranuclear clear zone may be present

KEY DIFFERENTIATING FEATURES

small to medium-sized mononuclear cells
relatively high nuclear-cytoplasmic ratio
round or oval nucleus
small inconspicuous nucleoli
light blue usually agranular cytoplasm

OTHER FEATURES

azurophilic granules in large granular lymphocytes
more basophilic cytoplasm and slightly eccentric nucleus in plasmacytoid lymphocyte

POTENTIAL LOOK-ALIKES

lymphoma cells, particularly small lymphocytic lymphoma (CLL), mantle cell lymphoma
lymphoblasts (in acute lymphoblastic leukemia)

NORMALLY SEEN

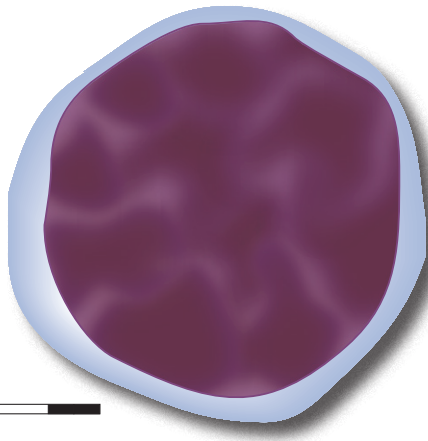
present in virtually all normal body fluids

ASSOCIATED DISEASE STATES AND CONDITIONS

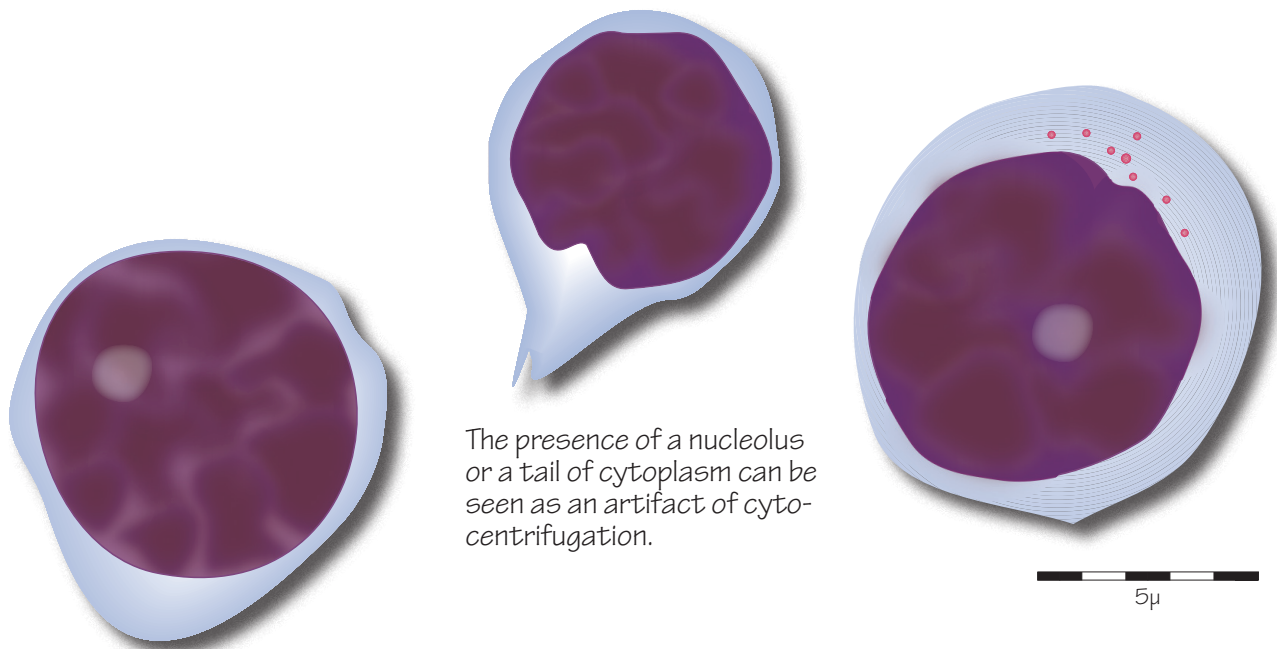
viral infection
tuberculosis
chronic inflammatory states
chylous effusions
congestive heart failure
cirrhosis
nephrotic syndrome
tuberculous peritonitis

Lymphocytes are mononuclear bone marrow-derived cells that are commonly found in normal body fluids. On most Wright-stained preparations, small lymphocytes appear slightly larger than erythrocytes but smaller than neutrophils and monocytes. The nucleus of most small lymphocytes is round to oval, although some may have an indented reniform shape, with clumped and densely basophilic chromatin, and a small inconspicuous nucleolus. The scant cytoplasm of the small lymphocyte is most often light blue and clear, although a few small irregular azurophilic granules may be present. Nearly all small lymphocytes in body fluids represent mature (TdT-negative) CD3/CD7-positive T cells or CD19/20-positive B cells. Other benign types of small lymphocytes, such as CD10-positive follicular B cells (centrocytes), CD5-positive mantle zone B cells, and marginal zone (monocytoid) B cells, are not found in normal body fluids. Changes in lymphocyte morphology induced by the cytocentrifuge include cytoplasmic spreading, nuclear convolutions, and nucleolar prominence. It is important not to interpret these features as of those of a lymphoma.

Large granular lymphocytes (LGL) are medium to large lymphocytes, nearly the size of monocytes, with a round to oval nucleus with clumped and densely basophilic chromatin, an inconspicuous nucleolus, and abundant light blue cytoplasm containing numerous small azurophilic granules. Large granular lymphocytes most often type as either true CD3-negative CD8-positive natural killer (NK) cells or CD3-positive CD8-positive NK-like cytotoxic T cells. Under normal circumstances, LGLs represent only a small proportion of the circulating lymphocyte pool. However, in some circumstances, such as viral infections, LGLs may constitute a larger proportion of the total lymphocytes in blood and body fluids. Plasmacytoid lymphocytes may sometimes be seen in body fluids, usually in the company of plasma cells. Plasmacytoid lymphocytes are small to medium-sized cells with relatively more abundant and more basophilic cytoplasm than small lymphocytes, an eccentric nucleus, and sometimes a small perinuclear clear zone (hof). Plasmacytoid B lymphocytes, in contrast to plasma cells, express CD20 and cell surface immunoglobulin (Ig).



Normal Mature Lymphocyte

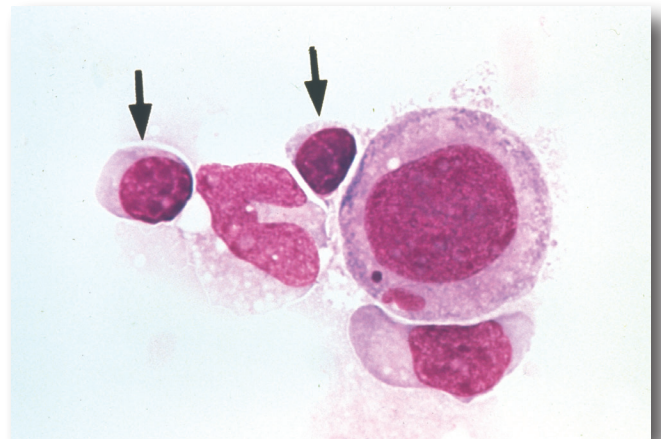


The presence of a nucleolus or a tail of cytoplasm can be seen as an artifact of cyto-centrifugation.

CM-24, 1995 (CSF, Wright-Giemsa, X400)

Identification	Referee %	Participant %
Lymphocyte	100.0	97.6
Lymphocyte, reactive	-	1.8
Plasma cell	-	0.2

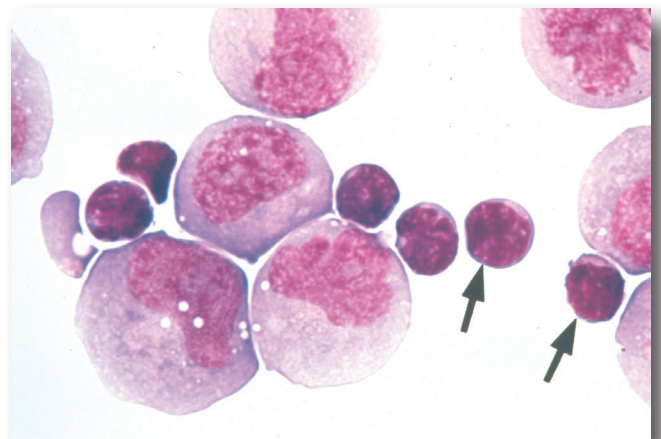
This cerebrospinal fluid was obtained from a 60-year-old woman with a lung mass and severe headache. The two arrowed cells are small lymphocytes. Note the presence of a small yet distinct light-staining nucleolus in the cell on the left—a normal feature often seen in body fluids. The larger cell between the lymphocytes is a monocyte, while the two remaining larger cells most likely represent malignant cells from this patient's lung adenocarcinoma.



CM-08, 1996 (Pleural, Wright-Giemsa, X400)

Identification	Referee %	Participant %
Lymphocyte	96.2	95.6
Lymphocyte, reactive	3.8	2.2

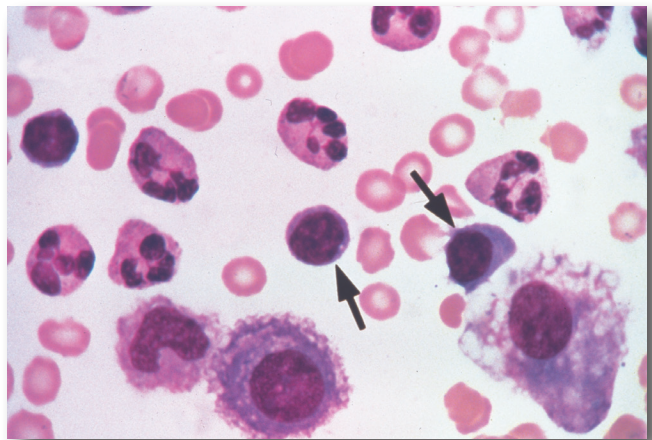
This pleural fluid was obtained from an 18-year-old woman with previously treated acute myelogenous leukemia (AML, M5B). The arrowed cells are small lymphocytes. These cells do not exhibit features of reactive lymphocytes, i.e., larger size with more abundant, often basophilic, cytoplasm. The much larger cells in this field are abnormal neoplastic promonocytes with lobulated nuclei, multiple small nucleoli, and abundant finely granular cytoplasm, consistent with AML-M5B.



CM-14, 1996 (Peritoneal, Wright-Giemsa, X320)

Identification	Referee %	Participant %
Lymphocyte	96.2	98.2
Mesothelial cell	3.8	0.1

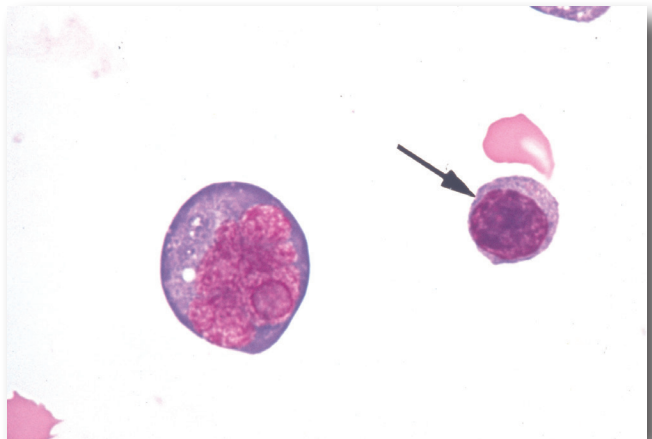
This peritoneal fluid was obtained from a 74-year-old man with congestive heart failure and ascites. Studies showed a WBC = 2850/ μ L, and RBC = 16,800/ μ L. The arrowed cells are small lymphocytes, one of which (on right) exhibits slight plasmacytoid features. The two larger cells near the bottom with ruffled cytoplasmic borders are mesothelial cells. There is a single monocyte with a horseshoe-shaped nucleus just to the left of one of the mesothelial cells. The remaining cells in the field are neutrophils.



CM-15, 1999 (Peritoneal, Wright-Giemsa, X400)

Identification	Referee %	Participant %
Lymphocyte	100.0	96.0

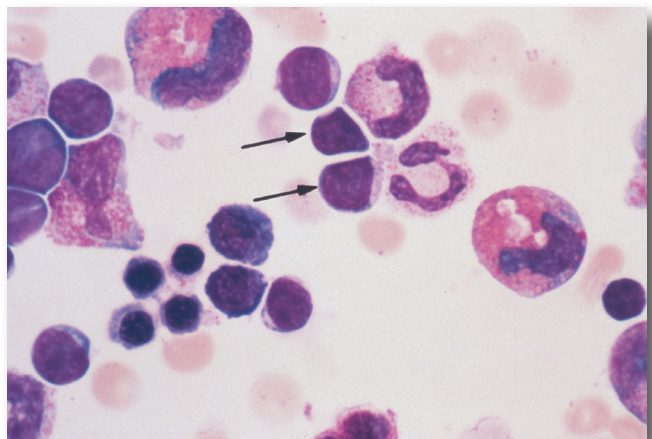
This peritoneal fluid was obtained from a 52-year-old man with a diagnosis of large cell lymphoma. Studies showed a WBC = 7500/ μ L, RBC = 4500/ μ L and albumin < 1 g/dL. The arrowed cell is a small lymphocyte. The larger cell in this field, with the basophilic cytoplasm, finely dispersed chromatin, and large nucleolus, is a lymphoma cell.



CM-25, 1999 (CSF, Wright-Giemsa, X330)

Identification	Referee %	Participant %
Lymphocyte	100.0	95.0
Lymphocyte, reactive	-	3.5

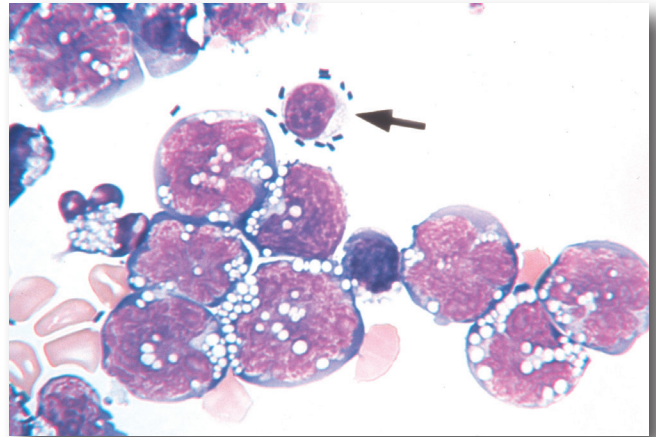
This cerebrospinal fluid was obtained from a 2-month-old boy with fever and irritability. Laboratory data includes: WBC = 176/ μ L and RBC = 1302/ μ L. The arrowed cells are small lymphocytes without reactive features. Also in this field (left of center) is a group of six erythroid precursors, four of which are smaller orthochromic normoblasts, and two of which are larger basophilic normoblasts. A few immature lymphoid cells are also present. Immature lymphoid cells (lymphoblasts) are sometimes encountered in the CSF of infants and children with reactive conditions.



CM-31, 1992 (Peritoneal, Wright-Giemsa, X330)

Identification	Referee %	Participant %
Lymphocyte	100.0	95.2

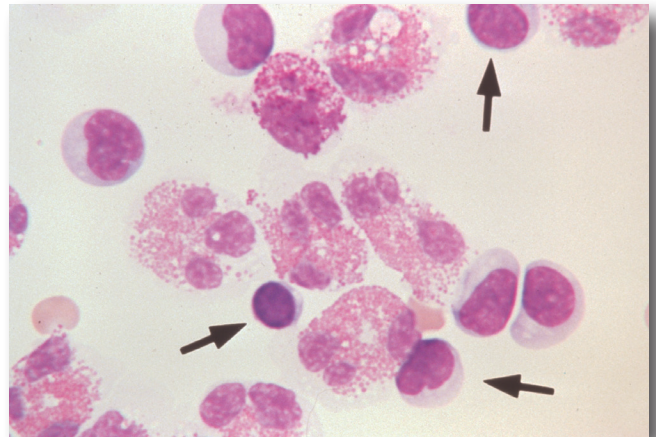
This peritoneal fluid was obtained from a 43-year-old woman with large cell lymphoma of the cecum. The arrowed cell is a small lymphocyte surrounded by rod-shaped bacteria. The cell is much smaller than the large vacuolated lymphoma cells. The nucleus is oval with coarsely clumped nuclear chromatin, absent nucleoli, and moderate amounts of relatively clear agranular cytoplasm typical of a small non-reactive lymphocyte. Below this cell and located between two tumor cells is a small lymphocyte with more basophilic nuclear chromatin and cytoplasm. This change may indicate either plasmacytoid differentiation or early apoptotic change.



CM-25, 1990 (CSF, Wright-Giemsa, X330)

Identification	Referee %	Participant %
Lymphocyte	100.0	96.1

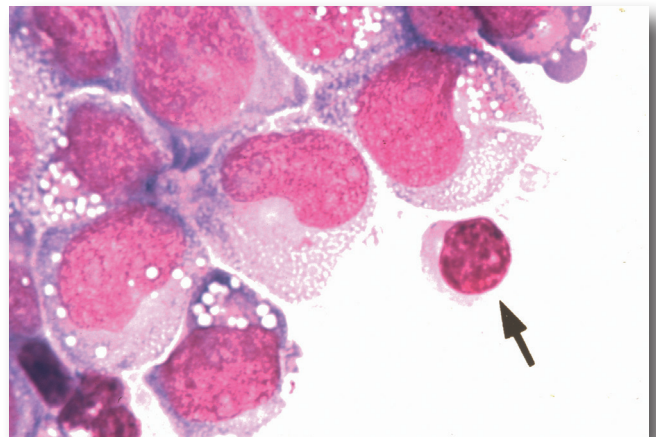
This cerebrospinal fluid was obtained from a 6-year-old boy with seizures living in a rural farming area of California. He emigrated to the U.S. from Mexico with his family two years ago. Studies showed a WBC = 408/ μ L, RBC = 156/ μ L, protein = 130 mg/dL, and normal CSF glucose. CSF WBC differential showed 72% eosinophils, 17% lymphocytes, 6% basophils, and 5% monocytes. Further workup led to a diagnosis of cysticercosis. The arrowed cells in this field are small mature lymphocytes. Slight indentation of normal lymphocyte nuclei can be seen in cytocentrifuge preparations.



CM-08, 1997 (Pleural, Wright-Giemsa, X400)

Identification	Referee %	Participant %
Lymphocyte	100.0	90.3
Lymphocyte, reactive	-	6.0

This pleural fluid was obtained from a 76-year-old female with a history of large cell lymphoma, successfully treated one year ago, but now with a recalcitrant pleural effusion. The arrowed cell is a small lymphocyte. The nucleolus seen in this cell is a normal finding, often seen as a result of cytocentrifugation. In contrast to the many lymphoma cells in this field, this cell is smaller with clumped nuclear chromatin typical of a small lymphocyte.



Lymphocyte, Reactive

SYNONYMS

atypical lymphocyte, plasmacytoid lymphocyte, immunoblast

VITAL STATISTICS

size	10 to 25 μm
n:c ratio	3:1 to 1:2
cell shape	oval to irregular
nuclear shape	oval to folded to lobulated
chromatin.....	ranging from fine to loosely clumped to coarsely clumped
nucleoli.....	not visible or may be multiple
cytoplasm.....	moderate to abundant; pale blue to deeply basophilic, often darker in periphery; paranuclear clear zone often seen in plasmacytoid variant; fine azurophilic granules may be seen; few vacuoles may be seen; peripheral scalloping around red cells may be seen

KEY DIFFERENTIATING FEATURES

medium to large mononuclear cells
round to oval, sometimes irregular nuclei
abundant pale to deeply basophilic cytoplasm

OTHER FEATURES

multiple nucleoli
peripheral cytoplasmic basophilia
cytoplasmic scalloping around adjacent erythrocytes
occasional vacuoles
few azurophilic granules

POTENTIAL LOOK-ALIKES

large cell lymphoma, B-cell or T-cell monocytes

OCCURRENCE IN BODY FLUIDS

not present in normal body fluids

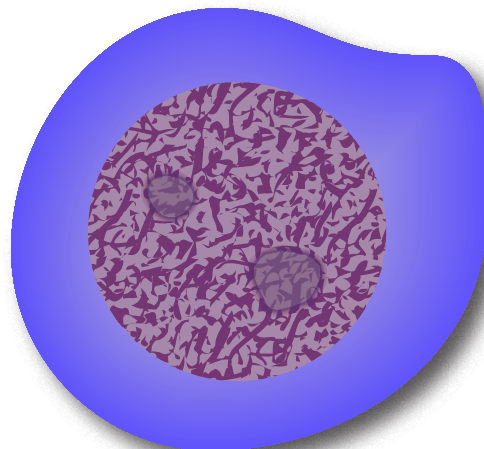
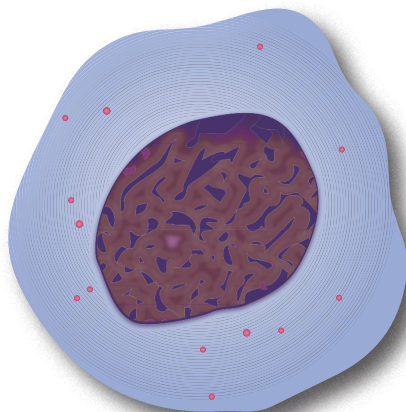
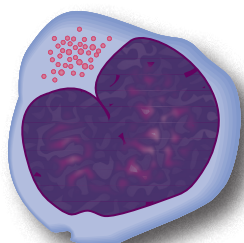
ASSOCIATED DISEASE STATES AND CONDITIONS

viral infections, especially acute EBV and CMV infection (mononucleosis)
chronic active inflammatory conditions (rare)

Most reactive lymphocytes seen in viral illnesses type as CD3/CD8-positive cytotoxic T cells. Plasmacytoid lymphocytes are medium-sized cells with irregular, densely clumped nuclear chromatin, absent to indistinct nucleoli, and moderately abundant basophilic cytoplasm, often with a paranuclear clear zone. Plasmacytoid lymphocytes nearly always type as mature post-germinal center B cells and express abundant cytoplasmic immunoglobulin. In contrast to plasma cells, reactive lymphocytes express the B cell surface antigens CD19 and CD20. Immunoblasts are large cells with round to oval nuclei, fine delicate chromatin, prominent nucleoli, and moderate amounts of deeply basophilic cytoplasm. Reactive immunoblasts may type as either T cells or B cells. In some cases, reactive immunoblasts may so closely resemble lymphoma cells or blasts that differentiation may require use of ancillary techniques such as immunophenotyping by flow cytometry for detection of an aberrant phenotype and molecular analysis for detection of clonal antigen receptor gene rearrangements.

The distinction between normal and reactive lymphocytes is often difficult and subject to considerable intra-observer disagreement. However, it is important to remember that, in either case, the underlying disease process is benign. It is much more important to distinguish reactive lymphocytes from lymphoma cells. In most cases, lymphoma cells display abnormal nuclear features not present in reactive lymphocytes. Also, while reactive lymphocytes in body fluids are morphologically diverse and often accompanied by a variety of other inflammatory cells, lymphoma cells are most often present as monotonous populations unaccompanied by other inflammatory cells.

Reactive Lymphocytes

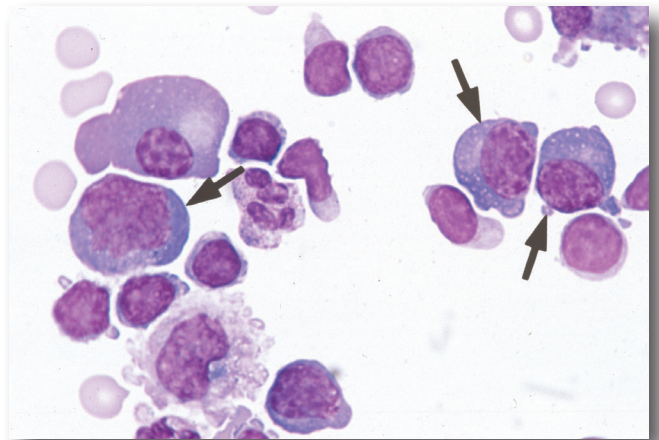


5 μ

CM-09, 2003 (Pleural, Wright-Giemsa, X320)

Identification	Referee %	Participant %
Lymphocyte, reactive	50.0	33.7
Plasma cell	25.0	22.6
Mesothelial cell	21.4	13.2
Lymphoma cell	3.6	1.1

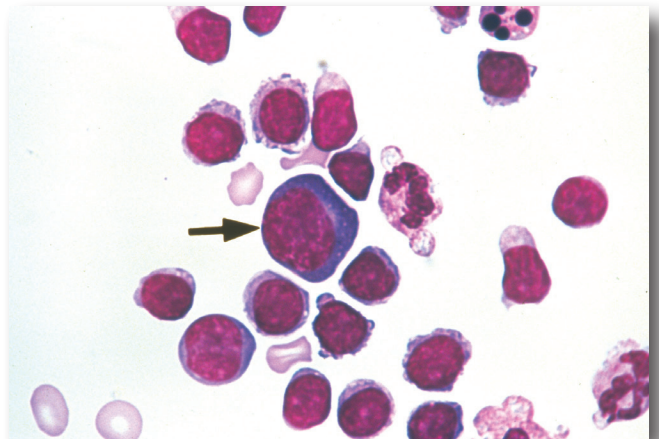
This pleural fluid was obtained from a 60-year-old male with newly diagnosed carcinoma of the left lung. WBC = 7400/ μ L and RBC = 4000/ μ L. The arrowed cells all represent atypical lymphocytes. Note the large size and cytoplasmic basophilia of these cells in comparison to the smaller lymphocytes. The two arrowed cells to the right have eccentric nucleoli and perinuclear clear zones, features of plasmacytoid lymphocytes. Also seen in this field are a plasma cell, a macrophage, and a neutrophil.



CM-97, 2003 (Pleural, Wright-Giemsa, X320)

Identification	Referee %	Participant %
Lymphocyte, reactive	60.7	41.1
Plasma cell	21.4	18.3
Mesothelial cell	10.7	11.2
Malignant cell (non-heme)	7.1	9.2

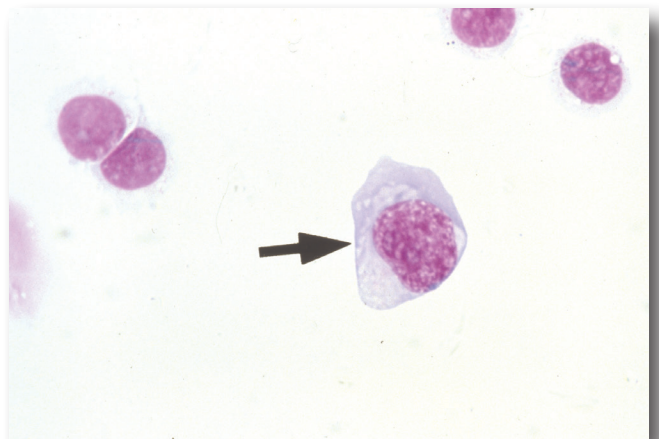
This photomicrograph is from the same case as CM-09, 2003, above. The arrowed cell in this field is an atypical lymphocyte. Note the larger size and cytoplasmic basophilia of this cell in comparison to the numerous smaller lymphocytes in this field. Two neutrophils are also seen.



CM-27, 2003 (CSF, Wright-Giemsa, X320)

Identification	Referee %	Participant %
Lymphocyte, reactive	84.6	51.5
Monocyte/macrophage	7.7	39.4

This CSF was obtained from a 58-year-old HIV-positive man experiencing progressive confusion and severe headache. The arrowed cell is a reactive lymphocyte, which is larger and has more cytoplasm when compared to a resting lymphocyte. While the nucleus appears slightly eccentric, it is oval in shape and demonstrates a more immature chromatin pattern as compared to a plasma cell. Small nucleoli are visible.





A Closer Look At...

How Reactive Lymphocytes Form

In blood, reactive lymphocytosis may be seen with numerous viral infections, a few bacterial infections (pertussis, brucella), hyperthyroidism, Addison's disease, inflammatory bowel disease, drug reactions, and vasculitis. Antigen-induced activation of normal lymphocytes causes transcriptional activation of several genes, resulting in proliferation as well as a variety of morphologic changes. In general, the activated lymphocytes become enlarged, with increases in volume of both nuclei and cytoplasm. The nuclear chromatin of reactive lymphocytes is less intensely basophilic than that of small resting lymphocytes, with alternating areas of lightly stained euchromatin and darkly stained heterochromatin. Reactive lymphocytes may sometimes have small nucleoli that can be misinterpreted as a sign of neoplastic change.

Reactive B lymphocytes may undergo plasmacytoid differentiation characterized by slightly eccentric nuclei, a very small perinuclear clear zone, and moderately abundant cytoplasm that is slightly pink-red due to the increased amounts of cytoplasmic immunoglobulin. Unlike plasma cells, plasmacytoid lymphocytes express the B cell antigen CD20 and express immunoglobulin not only within the cytoplasm but also on the cell surface, usually polyclonal IgG. They can sometimes be confused on purely morphologic grounds with the plasmacytoid B cells of Waldenström macroglobulinemia, which express monoclonal IgM.

Reactive lymphocytes are classically described in blood as large, activated, CD8-positive T cells with

abundant cytoplasm that may contain a few azurophilic granules. These cells often display irregular cytoplasmic borders that seem to scallop or mold around surrounding red blood cells, and the peripheral cytoplasm may stain a slightly darker blue than the perinuclear cytoplasm. The nuclear chromatin varies from clumped to finely granular, and nucleoli may be present. Causes of reactive lymphocytosis include infectious mononucleosis, viral hepatitis, viral pneumonias, varicella, CMV infection, pertussis, brucellosis, syphilis, toxoplasmosis, and drug reactions. In body fluids, reactive lymphocytes are not as easily differentiated from other reactive lymphocyte subsets, possibly due to centrifugation induced artifacts. Also, since reactive lymphocytes are classically associated with infectious mononucleosis—a disease that seldom is associated with effusions—they are not usually described or differentiated as distinctive in body fluids.

The distinction between reactive lymphocytes and malignant lymphocytes in body fluids is seldom difficult. Reactive lymphoid infiltrates, unlike malignant lymphoid infiltrates, typically are composed of a polymorphous collection of lymphocytes with an admixture of small lymphocytes and lesser numbers of plasmacytoid lymphocytes, reactive lymphocytes, and immunoblasts, as well as monocytes and granulocytes. Rarely, however, benign monomorphic collections of small lymphocytes may be seen. Examples include chylous effusions due to thoracic duct leakage, and infectious lymphocytosis.

Reactive Lymphocyte Formation

