Review Article

The Atypical Lymphocyte

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Abstract

The atypical lymphocyte is a reactive lymphocyte that plays an important role in the immune response. Blood analysis is moving toward automated differentials which may miss atypical lymphocytes. The presence and number of atypical lymphocytes are useful information and in certain situations diagnostic of specific disease states. *Int Pediatr. 2003;18(1):20-22.*

Key words: atypical lymphocyte, automated differentialsm, immune response

Introduction

With our current state of the art automated complete blood count and differential, the number or even presence of atypical lymphocytes is being under reported. We are losing important and, at times, vital information helpful in diagnosing different disease states in children. The atypical lymphocyte is a nonmalignant leukocyte seen in the peripheral blood. It is a reactive lymphocyte of lymphoid origin and produced in a variety of disorders (Table 1).[1-11] It appears to be a nonspecific response to stress from a variety of stimuli. A small lymphocyte becomes larger in size and capable of dividing.[12] It was originally described by Türk[13] ("Türk cell") in 1907 in the peripheral blood of patients with infectious mononucleosis and later classified in greater detail by Downey and McKinlay in 1923.[14] Today, it is called an atypical lymphocyte, Downey cell, or reactive lymphocyte and is a marker of illness when observed in a peripheral blood smear.

Morphology

Atypical lymphocytes vary in morphologic detail as well as surface marker characteristics showing that they comprise a heterogeneous mixture of cell types. This is the result of a polyclonal immune response to antigenic stimulation.[4] Morphology may differ from one case to another.[4] These lymphocytes are readily identifiable by their increased size and presence of active DNA synthesis.[4] They may look like a cross between a plasma cell and a lymphocyte and called a Plymphocyte, lymphocytoid plasma cell, or plasmacytoid lymphocyte.

Light microscopy shows that atypical lymphocytes vary in size and staining properties.[2,3,5] They are larger than a mature lymphocyte.[2,15] The cell may be indented at its periphery by the surrounding cells producing a scalloped appearance.[5] The cytoplasm is abundant and often vacuolated giving it a foamy appearance. When stained with either Wright's or Giemsa stain, the cytoplasm will vary in color being basophilic, dark blue, plasmacytic to pale gray.[2,5,15] It may be dark blue at the periphery of the cell. The nucleus is distinctive, often lobulated or indented. It may be oval, round, kidney-shaped, or divided and placed eccentrically.[5,15] It has slightly finer chromatin compared to a small lymphocyte.[15]

Histochemistry shows reactive lymphocytes to have increased concentrations of acid phosphatase, phosphorylase, and non-specific esterase.[17,18] They have a high glycogen content.[18] Pyroninophilia was weak and acridine orange fluorescence was absent indicating low cytoplasmic RNA content. Increased levels of formate-activating enzymes N^5 N^{10} methyltetrahydrofolic dehydrogenase and dihydrofolic reductase occurred in atypical lymphocytes. Glucose-6 phosphate dehydrogenase activity is reduced.[16] This information is consistent with reactive lymphocytes synthesizing DNA.[17]

Electron microscopy has revealed a number of ultramicroscopic properties of atypical lymphocytes.[4,17] Endoplasmic reticulum, the Golgi apparatus and other organelles show different degrees of development. The endoplasmic reticulum is sparse. There is finely reticular nuclear chromatin, long thin frequently

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Table 1 - Causes of Atypical Lymphocytosis

Infection	**Drug and Toxic Reactions**	**Autoimmune Disorders**
Epstein-Barr virus	Hydantoin drugs (Dilantin)	Rheumatoid arthritis
Cytomegalovirus	Para amino salicylic acid (PAS)	Idiopathic thrombocytopenia purpura
Toxoplasma	Phenothiazine	Systemic lupus erythematosus
Q fever	Organic arsenicals	Autoimmune hemolytic anemia
Rubella	Lead	Chronic hepatitis
Roseola	Trinitrotoluene	Agammaglobulinemia
Herpes simplex	Diaminodiphenyl-sulfone (dapsone)	
Hemorrhagic fever		
Herpes zoster	**Postperfusion syndrome**	**Malignant Disease**
Rickettsial pox		Hodgkin's Disease
Rubeola	**Immunizations**	
Mumps		**Idiopathic Disorders**
Adenovirus	**Radiation**	Sarcoidosis
Influenza		Carcinomatous neuropathy
Tuberculosis	**Hormonal Causes**	Guillain-Barre syndrome
Varicella	Stress (epinephrine)	Myasthenia gravis
Syphilis	Addison's disease	Acute disseminated encephalomyelitis
HIV (1+2)	Deficiencies of glucortocoids	
Hepatitis A	Panhypopituitarism	**Graft Rejection**
Hepatitis B	Thyrotoxicosis	Renal
Adenovirus		
Listeria monocytogenes		
Dengue hemorrhagic fever		
Mycoplasma pneumonia		

branched mitochondria, and a well-developed Golgi apparatus.[12,17]

There are prominent clusters and rosettes of free ribosomes.[12] Some cells have many cytoplasmic RNA granules.[17] Small vacuoles near the edge of the cytoplasm as well as invaginations in the cell surface suggests micropinocytosis. This is seen in cells undergoing DNA synthesis. Autoradiographic studies using tritiated thymidine confirms atypical lymphocytes are actually synthesizing deoxyribonucleic acid.[19-21] Similarly tritiated cytidine shows reactive lymphocytes are synthesizing RNA.[20]

Function

The ubiquity of the reactive lymphocyte suggests it plays an important role in the immune response. The atypical lymphocytes have been best studied from blood of patients with infectious mononucleosis. A variety of early studies using incorporation and radioautography with tritiated thymidine and rosette formation demonstrated that atypical lymphocytes are heterogeneous having both T and B cell types.[4,6,22] Their heterogeneity in cells suggests they are reactive in nature. These studies also confirm that they are actively proliferating.[15] Antigenic stimulus leads to a polyclonal proliferation lymphoid response.[4,6]

More recent studies suggest the reactive lymphocytes are activated T-lymphocytes produced in response to infected B-lymphocytes.[23,24] Atypical lymphocytes are rosette forming with sheep red blood cells confirming they are T lymphocytes that have undergone transformation.[23,24,26] It is possible that some of these cells identified as B-cells are actually T-cells coated with autoantibody. However, a study by Pattengale et al showed that atypical lymphocytes had sheep erythrocyte receptors as well as human T-cell specific antigens and lacked B-cell receptors, i.e., complement receptors, surface immunoglobulin, and human B-lymphocyte specific antigens.[27]

Reactive lymphocytes have been found to accumulate in areas of inflammation like the liver and pharynx of individuals with infectious mononucleosis and skin window preparations.[28] They act as normal lymphocytes in sites of local inflammation, playing a role in the immune response in a primary cellular immune or helper T-cell response. Cell-mediated immunity is important in the host defense against viral infections and control of malignant neoplasia. In infectious mononucleosis, the atypical lymphocytes are one component of a normal immune system that helps to control potentially fatal Epstein-Barr virus-induced B-cell lymphoma in man.[29-31] They are produced by antigenic challenge by infections, after immunizations,

rheumatoid arthritis, and systemic lupus erythematosus.[19]

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