

## Case Report

# Diagnosing Infections from the Peripheral Blood Smear

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### Abstract

Examination of the peripheral blood smear is probably an under-utilised laboratory investigation in clinical practice. Three illustrative cases are presented in which reading of the blood smear provides important clues that directly lead to the identification of the infective agents. In the first case, a male neonate with thrombocytopenia at birth manifested polymorphic atypical lymphocytosis. Perinatal cytomegalovirus infection was suspected and was confirmed when the viral DNA was detectable in the plasma. In the second case, a 7-month-old girl was admitted with respiratory distress and signs of pneumonitis. Lymphocytosis with atypical cells showing convoluted nucleus strongly indicated pertussis, which was confirmed when *Bordetella pertussis* DNA was found from the nasopharyngeal swab. In the third case of a 16-year-old boy who presented with a 3-month history of fever and diarrhoea, the finding of atypical lymphocytosis with abundant large granular lymphocytes pointed to the diagnosis of infectious mononucleosis. This was confirmed when Epstein-Barr virus DNA was found in the plasma. With appropriate management, all recovered from their primary symptoms/signs. Examination of the peripheral blood smear can be a powerful adjunct to guide diagnostic tests and to refine the use of antibiotics in the management of childhood infections.

### Key words

Complete blood count; Cytomegalovirus; Infectious mononucleosis; Peripheral blood smear; Pertussis

### Introduction

Complete blood count (or full blood count) is the most commonly ordered blood test in clinical practice,<sup>1</sup> especially in hospitalised children. Modern automated blood cell counters can accept as little as 0.2 mL of anticoagulated blood and produce a detailed report on red cells, white cells and platelet, with differential white blood cell counts. A drop of the remaining blood is then smeared and stained. Depending on the hospital or laboratory policy, peripheral

blood smears are only read if there are qualifying clinical indications, the automated blood cell counts are abnormal, or if there are alarming flags raised by the automated counter.

In the evaluation of a febrile child or when an infection is suspected, the automated complete blood count report provides a total white blood cell (WBC) count and a 5-cell differential. The differential includes neutrophil, lymphocyte, monocyte, eosinophil and basophil. In addition, there is an extra column of large unstained cell (LUC) that contains cells the automated counter fails to differentiate. Based on the proportion and absolute counts of the neutrophil and lymphocyte, the clinician may be able to grasp the likelihood of a bacterial versus a viral illness. The automated report, however, does not provide clues for any specific infection.

The peripheral blood smear can provide further details about the qualitative changes in the circulating blood cells.<sup>2</sup> Some of these changes, such as left shift in the granulocytes and cytoplasmic changes in the neutrophil, may strongly

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favour a diagnosis of bacterial sepsis. Other changes in the lymphocytes may provide important hints to more specific bacterial or viral pathogens.

## Case Reports

### Case 1

A term infant with a birth weight of 2.2 kilogram was born to an Indian couple. He was admitted to the special baby care unit because of transient tachypnoea. Besides the small size, the clinical examination was unremarkable. The complete blood count done shortly after birth showed normal haemoglobin and total WBC but thrombocytopenia (platelet,  $44 \times 10^9/L$ ). Examination of the peripheral blood smear revealed 20% of atypical lymphocytes with various morphology and atypical mononuclear cells with cytoplasmic vacuoles. The haematological findings were most suggestive of perinatal cytomegalovirus (CMV) infection. Quantitative polymerase chain reaction for CMV-DNA confirmed the diagnosis with  $1.53 \times 10^5$  copies/mL in the plasma. Chorioretinitis was absent but hearing screen by otoacoustic emissions was not successful. He was discharged on day 10 of life and referred to an otorhinolaryngologist for hearing assessment.

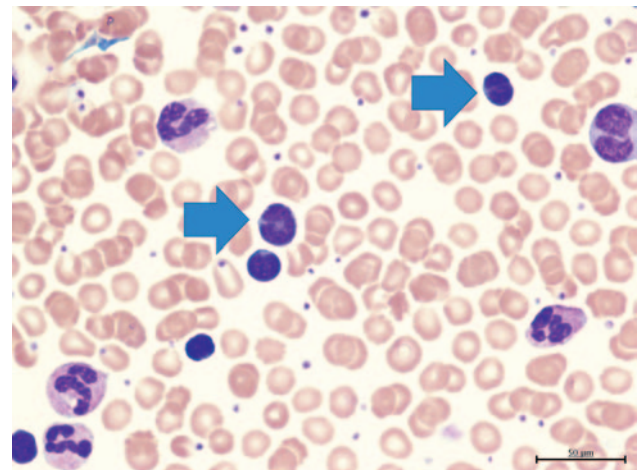
### Case 2

A 7-month-old Italian girl residing in Jakarta was medically evacuated to our hospital because of progressive respiratory distress and the finding of marked leukocytosis on complete blood count. The child had not been well for a week. She was admitted to the local hospital because of tachypnoea and blood tests revealed a total WBC of  $98 \times 10^9/L$ . Blood dyscrasia was suspected and hence the emergency transfer of the child. Intravenous ceftriaxone was started prior to evacuation. On admission, her temperature was  $38^\circ C$ . Fine crepitations were audible from both sides of the lungs. Lymphadenopathies were not found. The liver and spleen were just palpable below the costal margins, which were probably secondary to hyper-inflation of the lungs. The complete blood count showed Hb 12.4 g/dL, WBC  $77.14 \times 10^9/L$ , platelet  $812 \times 10^9/L$ . Under the microscope, 10% of the WBC were atypical lymphocytes. Fifteen percent of the lymphocytes showed abnormal nuclear folding with convolution (Figure 1). A few showed radial segmentation. No malignant cells were seen. These changes, in addition to absolute lymphocytosis ( $34.7 \times 10^9/L$ ), were

typically seen in pertussis infection. Oral azithromycin was added. The report of the nasopharyngeal swab came back later positive for *Bordetella pertussis* DNA. A slow but complete recovery ensued.

### Case 3

A 16-year-old American boy was residing in Java with his missionary family. For the past 3 months, he had been noted to be lethargic from time to time with repeated febrile episodes and temperatures as high as  $39^\circ C$ . Blood tests and chest radiograph were unrevealing. His symptoms persisted despite several courses of oral antibiotics. In the preceding month, he started to have diarrhoeal symptoms and some subjective weight loss. His condition was stable on examination. No significantly enlarged lymph node, liver or spleen could be found. There was no obvious focus of infection either. An inflammatory bowel disease was initially suspected. The stool was watery with some leukocytes, but bacteria, rotavirus, and parasites were not found. Stool calprotectin was not increased. The complete blood count, however, showed, Hb 14.6 g/dL, WBC  $12.7 \times 10^9/L$  and platelet  $178 \times 10^9/L$ . The peripheral blood film revealed 25% of atypical lymphocytes. Half of these were large granular lymphocytes (Figure 2). The haematological findings were consistent with infectious mononucleosis. Epstein-Barr virus DNA at a concentration of 21,000 copies/mL plasma was found. Antibiotic treatment was stopped and attention was directed to fluid and nutritional support. His symptoms completely resolved a month later.

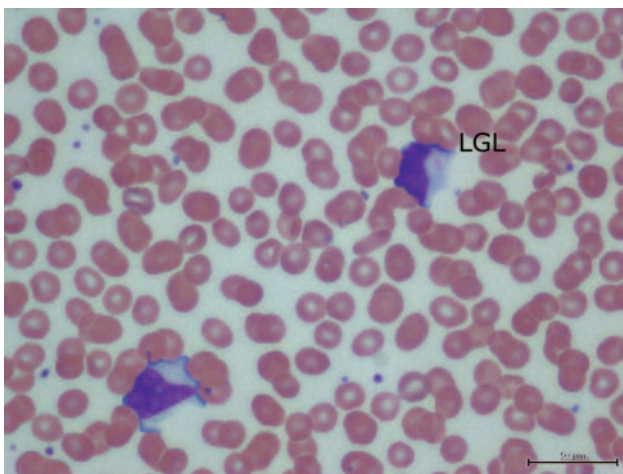


**Figure 1** Atypical lymphocytes in the 7-month-old girl (Case 2) showing nuclear clefts and convolutions (marked by arrow).

## Discussion

With manual spread of a drop of blood on a glass slide and automated staining system, the preparation of a peripheral blood smear is a simple and fast procedure in the laboratory. Yet the morphological information it provides is rich. For certain haematological disorders, for instance leukaemia, examination of the peripheral blood smear can be diagnostic. For others, the peripheral blood smear provides important clues in the clinical management and determines which diagnostic tests are indicated.<sup>2</sup>

Clinicians often refer to the complete blood count with differentials when evaluating patients with fever and infectious diseases. The blood smear provides qualitative, morphological changes that are not obvious on the automated report from the analyser. Similar to haematological conditions, the peripheral blood smear can be diagnostic of parasitic infections.<sup>3</sup> Morphological changes in the granulocytes are often regarded as important, though nonspecific, clues for an occult bacterial infection. The appearance of immature precursors, often referred to as "left shift", or cytoplasmic changes in the neutrophils such as toxic granules, vacuoles, and Dohle bodies are often regarded as signs of bacterial sepsis. Fragmented red cells or schizocytes are the hallmark of microangiopathy, and may be a sign of disseminated intravascular coagulation in severe sepsis.



**Figure 2** Large granular lymphocytes (LGL) seen in the 16-year-old boy (Case 3). They are either T-lymphocytes or natural killer cells. On the left is an atypical lymphocyte that is a larger cell than normal lymphocyte, has plenty cytoplasm, and with cell border indented by surrounding red cells.

In contrast to the granulocytes, morphological changes in lymphocytes may give more specific clues as to the infecting agents. Atypical lymphocytes are reactive changes often found in viral infections and immune disorders.<sup>4</sup> When present in significant proportion (more than 10%), it is coined infectious mononucleosis and is characteristically seen after infection with the herpesviruses. Epstein-Barr virus infection is the classical example and CMV infection is another, as illustrated in Cases 1 and 3 in this report. In immunocompromised patients, large granular cells spread at the feathered end of the blood smear have been shown to be CMV-infected cells.<sup>5</sup> In contrast to other bacterial infections, *Bordetella pertussis* induces both neutrophilia and lymphocytosis. The quantitative changes in lymphocyte count are secondary to lymphocytosis-promoting factor, one of the several toxins produced by the bacteria. The morphological changes of the reactive lymphocytes that include nuclear clefts and convolutions, however, are poorly understood.<sup>6,7</sup>

In most laboratories, the reading of the peripheral blood smear is no longer routine. Criteria that incorporate clinical information, numerical deviations in the automated counts, and flags raised by the analyser are often employed to determine which smears are to be read manually. Guidelines from the International Society for Laboratory Hematology are a useful reference.<sup>8</sup> Hence, clinicians looking after children with infectious diseases have to inform the laboratory for the manual examination of the peripheral blood smear if they want to look for morphological clues.

In summary, examination of the peripheral blood smear or film is a useful adjunct in the laboratory evaluation of infectious diseases, but administrative and technical constraints may limit its application.

## Declaration of Conflicts of Interest

None

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