**HAEMATOLOGY 4
ABNORMAL WHITE CELL COUNT**

**Dr. Donald Macdonald** (d.h.macdonald@imperial.ac.uk)

## Learning Objectives

* In a leucocytosis (increased white cell count) explain the importance of the differential count and peripheral blood morphology in planning further investigation.
* List the most common causes of an increased neutrophil, eosinophil and lymphocyte count.
* In a lymphocytosis explain how to distinguish between a reactive polyclonal response to infection and a primary lymphoproliferative disorder (a monoclonal or malignant proliferation of lymphocytes such as chronic lymphocytic leukaemia).

The Full Blood Count (FBC) is a frequently requested investigation, which yields much useful information. This includes a total White Cell Count (WBC) along with an analyser generated white cell differential count. It is vital to consider both the total WBC and the differential count. There are limitations in the machine differential count particularly when abnormal white cells are present. It is therefore often necessary to examine the peripheral blood film microscopically to identify morphological features.

White cells consist of two main groups:

1) Phagocytes; including monocytes and granulocytes, the subtypes of the latter including neutrophils basophils and eosinophils

2) Immunocytes; which consist of T and B lymphocytes. These cell types will react in response to different stimuli.

Both cell groups are present throughout body tissues and play a central role in the response to infection mediated via phagocytosis and soluble proteins of the immunoglobulin and complement system.

**Investigating a leucocytosis (raised WBC)**

When an elevated WBC is identified it is necessary to first look at the automated differential. Is the leucoytosis due to an elevation of a particular cell type i.e. an increase in one cell type only e.g. a lymphocytosis, a neutrophilia or an eosinophilia, or alternatively an increase in all cell types. The next stage is to examine the blood film. This will provide further information such as whether only mature cells are present in the peripheral blood (PB) or immature forms such as myeloblasts and lymphoblasts (precursor/immature blood cells, normally confined to the bone marrow and not seen in peripheral blood except in diseases of the marrow such as leukaemia) are present. Morphology will also identify other features, including reactive changes such as toxic granulation in neutrophils. This approach allows correctly planned further investigation. For example an elevated total white cell count due only to the presence of mature eosinophils might suggest an underlying parasitic infection, whereas an elevated total white cell count due to the presence of immature blast cells, identified by microscopy suggests an underlying leukaemia.

# Important causes of elevated white cell counts

**Neutrophilia**

Neutrophilia is defined as an absolute neutrophil count > 7.5x109/l (adults.)

Common explanations for a neutrophilia seen in clinical practice are

* Bacterial infection. Probably the commonest cause is an acute bacterial infection e.g. chest, or urinary tract. The neutrophil count is raised and morphology may show toxic granulation. The presence of increased numbers of cytoplasmic granules and vacuoles.
* Inflammation and tissue necrosis e.g. appendicitis, myocardial infarct auto-immune tissue damage.
* Underlying neoplastic disease such as carcinoma or lymphoma may produce a reactive neutrophilia due to the aberrant production of stimulatory cytokines.
* Myeloproliferative disorders such as chronic myeloid leukaemia (CML) (also known as chronic granulocytic leukaemia – CGL) With CML, less mature forms such as myelocytes and rarely myeloblasts are present and basophilia is usually present
* Demargination: neutrophils within the blood stream are divided between the circulating and the marginated granulocyte pool. Physical exercise and acute, severe physical stress can increase the circulating neutrophil count by moving neutrophils from the endothelial surface of small blood vessels into the flowing blood. Corticosteroids raise the neutrophil count by other mechanisms.

# Eosinophilia

An eosinophil count of > 0.4 x109/l is designated an eosinophilia. The most common causes in different parts of the world are

* Parasite infestation e.g. schistosomiasis, filariasis.
* Atopic allergic conditions such as eczema and asthma
* Pulmonary eosinophilia.
* Hodgkin’s disease a cancer of the lymphatic system which may produce a reactive eosinophilia.

# Monocytosis

Monocytosis is uncommon but may be seen in certain chronic bacterial infections, which do not produce a neutrophil response, such as tuberculosis, brucellosis and typhoid. It may also occur in chronic myelomonocytic leukaemia.

Response to pyogenic bacterial infection

**Increase in cell numbers**: Infection by pyogenic bacteria will result in tissue damage and the production and release of a range of inflammatory cytokines. Amongst these may be factors such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) that will stimulate granulocyte and monocyte production by the bone marrow. More importantly in the acute response there will be the early release from the BM of less mature cells. This will result in an increase in the circulating granulocyte count and a left shifted appearance in the peripheral blood.

**Chemotaxis**: The phagocytes will circulate in the peripheral blood, at the site of infection they will move out of the circulation and into the tissues moving to the site of inflammation in response to chemotactic factors.

**Phagocytosis**: The neutrophils and monocytes will encounter foreign material that has been opsonised by immunoglobulin or complement. Using their Fc C3b receptors they are able to recognise and phagocytose the foreign material.

**Killing and digestion**: Ingested material will be killed within the phagocytic vacuoles by both oxidative and non-oxidative mechanisms.

# Lymphocytosis

A lymphocyte count > 4.0 x 109/l (adults) There are many causes of a lymphocytosis however they can be divided into two categories. Primary lymphocytosis, a malignant clonal proliferation of lymphocytes e.g. lymphocytic leukaemia, or lymphoma. Secondary reactive lymphocytosis a polyclonal reactive proliferation as a result of infection or inflammation.

# Reactive lymphocytosis

* Infections: Epstein Barr virus (EBV), Cytomegalovirus (CMV), Toxoplasma, Rubella, Adenovirus, Varicella-Zoster, Infectious Hepatitis, Pertussis, Tuberculosis, Brucellosis.
* Autoimmune disorders.

When a lymphocytosis is identified in a FBC the blood film must be examined for the presence of

* Atypical/reactive lymphocytes seen in mononucleosis syndromes.
* Immediate response to acute stress (e.g. heart attack or other severe pain).
* Small lymphocytes and smudge cells seen in chronic lymphocytic leukaemia.
* Primitive blasts seen in acute lymphoblastic leukaemia.

# Distinguishing between primary and reactive/secondary lymphocytosis

A full blood count may reveal the presence of an increased lymphocyte count. This can broadly be considered to be due to either a neoplastic proliferation of lymphocytes (a form of lymphoma or lymphoid leukaemia) or, alternatively, it may be a reaction to an underlying disorder such as a viral infection, for example ‘glandular fever’ (infectious mononucleosis). The approach to diagnosing the cause of a lymphocytosis would consider the age, clinical features and laboratory investigation. In the laboratory, morphology may simply reveal mature lymphocytes. The presence of abnormal forms such as smear cell (lymphocytes damaged by blood film preparation) or blast cells are suggestive of a lymphoproliferative disorder such as leukaemia or lymphoma. If required, further laboratory tests can distinguish between monoclonal (primary) and polyclonal (reactive) lymphocytes. Individual B lymphocytes express either κ or λ light chains on the cell surface. In a population of monoclonal B cells only one immunoglobulin light chain type, either κ or λ will be present whereas in a reactive increase in B cells there will be a mixed population of κ and λ expressing cells. A more demanding assay using the T cell receptor genes can be used to study the rarer finding of a T cell lymphocytosis.