This newsletter deals with an approach to increased white cell counts. All reference levels mentioned apply to adults.

Is an increased white blood cell count a clonal (malignant) or reactive increase?

This question is often asked, and in most cases the increase is reactive in nature. But be aware of the possibility of malignancy so that a potentially serious condition is not overlooked.

When a raised white cell count is detected, the differential count should always be evaluated to determine the significance of the high count. If the raised count is due to the presence of blasts or primitive mononuclear cells, particularly with associated cytopaenias, urgent evaluation by a haematologist is necessary.

1. **Neutrophilia**

A neutrophilia is one of the most common abnormal findings on the full blood count. This is defined as a neutrophil count greater than 8x10^9/l. There are numerous reactive causes of neutrophilia:

- **Steroid/stress response**
  
  Conditions associated with steroid and stress-hormone release can cause a rapid, usually transient, neutrophilia, for example, pain, exercise, seizures and emotional stress such as anger. This is primarily the result of redistribution of cells from vascular beds (e.g. the spleen) to the circulating pool.

- **Infection**
  
  Bacterial infection, particularly, is a common cause of neutrophilia. Associated changes to the neutrophil morphology may be noted on review of the peripheral smear. These include toxic granulation and vacuolation, the presence of dohle bodies and left shift. Rarely, organisms can be visualised within the neutrophils. In cases which are not clear, reactive markers such as CRP, procalcitonin and ESR may be useful in confirming inflammation.

- **Tissue infarction/necrosis**
  
  For example, myocardial infarction, burns and pulmonary embolism.

- **Chronic inflammation**
  
  Numerous chronic inflammatory conditions can be associated with chronic neutrophilia, for example, rheumatoid arthritis and dermatitis.

- **Drugs and toxins**
  
  - Exogenous steroids have multiple mechanisms for causing neutrophilia
  - Growth factor administration: e.g. neupogen (GM-CSF) therapy
  - Lithium
  - Chronic cigarette smoking: common cause of chronic neutrophilia

- **Underlying carcinoma or lymphoma**
  
  Certain carcinomas, particularly adenocarcinomas that have metastasised, can result in raised neutrophil counts, possibly through release of growth factors. This can be a cause of particularly high counts (over 100x10^9/l).

  More rarely lymphomas, for example Hodgkin's lymphoma, may stimulate a reactive increase in neutrophils.
Others

- Persistent neutrophilia may be detected post-splenectomy
- Chronic haemorrhage and haemolysis
- Rebound following agranulocytosis.

Clonal/malignant increase in the neutrophil count

This is far more rare than reactive causes. A clonal increase in a differentiated myeloid cell, such as the neutrophil, may occur in the myeloproliferative neoplasms. Findings that may increase suspicion of a myeloid malignancy include the presence of a significant left shift (neutrophil precursors in the peripheral blood), an associated increase in the basophil count, normal reactive markers, increased patient age, very high white cell counts (although there is no absolute cut off to distinguish reactive from clonal states), the presence of splenomegaly and accompanying thrombocytosis and/or polycythaemia. If there is concern, review of the peripheral smear is essential.

2. EOSINOPHILIA

An eosinophilia is defined as an eosinophil count above 0.5x10^9/l. A wide range of conditions can be associated with eosinophilia, some common, others less so. Eosinophilia may be reactive to an underlying condition or clonal (i.e. represent part of a malignant clone). A persistent significant eosinophilia can result in end organ infiltration and damage. The causes of eosinophilia are as follows:

Parasitic infection

This is the most common cause of eosinophilia worldwide. Helminthic parasitic infestation is a particularly common cause and can be associated with very high while blood cell counts.

Allergic disease

In the developed world, eosinophilia is more frequently seen secondary to atopic disease such as seasonal rhinitis, asthma and atopic dermatitis.

Drug reaction

Many drugs may be implicated and the eosinophil count returns to normal once the drug has been withdrawn. The drugs often involved are carbamazepine and minocycline.

Less common causes

Vasculitides and connective tissue disease are less common causes. In the case of malignant disease eosinophilia may be reactive to underlying non-haemopoietic tumours or lymphoma (e.g. Hodgkin’s lymphoma). Clonal T cell populations have been identified in a subset of patients with otherwise unexplained eosinophilia.

Clonal causes of eosinophilia

These are uncommon. Clonal eosinophilia may be seen in the context of myeloid and lymphoid neoplasms. Reactive causes should be excluded. In certain cases no reactive cause or evidence of clonality can be identified to explain a persistent eosinophilia. These cases have been labelled as idiopathic hypereosinophilic syndrome. This is an unexplained eosinophilia of >1.5x10^9/l that lasts for at least six months.

3. BASOPHILIA

This is a basophil count greater than 0.2x10^9/l. An increase in the basophil count can be noted in allergy and in inflammatory conditions such as ulcerative colitis. Viral infection, notably chickenpox and influenza, may have an associated basophilia.

Basophilia can be seen in clonal myeloid disorders. Importantly, CML (chronic myeloid leukaemia) is almost invariably associated with an increase in the basophil count. This can provide a clue to the diagnosis in patients with a neutrophil leucocytosis and left shift.

4. MONOCYTOSIS

A monocytosis is defined as a blood monocyte count greater than 1x10^9/l. An acute mild increase in the monocyte count can be recorded following acute physical and/or emotional stress (probably secondary to catecholamine release). This is as a result of demargination (redistribution from areas such as spleen, pulmonary capillaries). The increase is transient and is mirrored by an increase in the neutrophil and lymphocyte count.

A sustained increase is more significant. Conditions associated with monocytosis include infectious and other inflammatory disorders and malignant disease. A monocytosis can be reactive to the malignant disease or may be part of the abnormal clone. Reactive causes will be discussed first.
Infection

- Subacute/chronic: tuberculosis, bacterial endocarditis, syphilis
- Viral: CMV, VZV

Inflammatory conditions

Collagen vascular disease: systemic lupus erythematosus, rheumatoid arthritis etc.

Reactive to underlying malignancy

Monocytosis may be a marker of underlying malignancy and a reactive increase is seen in up to 60% of non-haemopoietic tumours.

Up to 25% of Hodgkin's lymphoma is associated with a monocytosis. It can also be noted in other lymphoproliferative disorders including multiple myeloma.

Others:

- Neutropaenic states such as cyclic neutropaenia or the early stages of drug-induced agranulocytosis may be associated with a monocytosis.
- Splenectomy

Clonal increase in monocytes (haemopoietic malignancy)

An increase in monocytes may be seen in certain acute myeloid leukaemias and chronic disorders such as particular myeloproliferative neoplasms and myelodysplastic syndromes. In some situations the monocyte count may be very high. Peripheral blood findings, including the presence of cytopenias and clinical features such as splenomegaly provide valuable clues in the investigation of an unexplained monocytosis. Assessment of inflammatory markers (e.g. CRP) should be considered. In certain cases a bone marrow investigation will be of value.

5. LYMPHOCYTOSIS

This is an absolute lymphocyte count of greater than 4x10^9/L. The increase may be reactive (polyclonal) or monoclonal. Clinical history and thorough physical examination, as well as assessment of the peripheral smear, are useful in differentiating between these two states.

Reactive causes of lymphocytosis

- Infectious mononucleosis type syndromes: Epstein-Barr virus, cytomegalovirus, HIV, toxoplasmosis etc
- Bordetella pertussis
- Chronic inflammation can result in a persistent increase, e.g. autoimmune disease
- Cigarette smoking
- Hypersensitivity reactions: drug reactions, delayed hypersensitivity to insect bites
- Splenectomy/hyposplenism
- Stress (acute) lymphocytosis: similar causes to acute neutrophilia and monocytosis

Malignant/Monoclonal lymphocytosis

Clinical features which can suggest a lymphoproliferative disorder include lymphadenopathy, hepatomegaly or splenomegaly, an isolated mass or findings such as unexplained skin lesions. If the morphology is unhelpful, the lymphocytosis persists or the clinical suspicion is high, flow cytometric analysis can be performed on a peripheral blood sample. This allows more definitive assessment of lymphocyte clonality.

B cell/T cell and NK cell lymphoproliferative disorders can be associated with a lymphocytosis.

6. BLASTS

The presence of a population of blasts or primitive mononuclear cells in the blood is usually a cause for concern. Please note that circulating blasts can be seen in the context of a reactive neutrophil left shift, but the number is usually small in comparison to the presence of maturing granulocytic elements.
If blasts or an abnormal primitive population are identified in the peripheral blood, flow cytometric analysis can be performed on this sample to further characterise the cells.

**CONCLUSION**

The presence of a raised white cell count should not be assessed in isolation. The component of the differential that is increased should be established. The presence of cytopaenias or other cytoses may provide additional information. Assessment of the peripheral blood smear by a haematologist or an experienced technologist may be of value in situations in which the cause of the increased count is not clear. Clinically, hepatosplenomegaly, lymphadenopathy and other abnormal masses should be excluded. In certain situations, a bone marrow investigation may be required. When an unexplained lymphocytosis is detected or blasts are present in the peripheral blood, flow cytometric analysis can be performed on a peripheral blood sample to investigate a possible haemopoietic/lymphoid malignancy.

**References**
