Investigating the patient with a raised white cell count

Each month we present authoritative advice on the investigation of a common clinical problem, specially written for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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With the proliferation of pathology testing, it is common to find pathological abnormalities of uncertain significance and be faced with the dilemma of whether to investigate these further. Within the area of haematology, the common abnormalities that fall into this category are mild anaemia, paraproteinaemia, mild thrombocytopenia (i.e. a platelet count of 100 to 150 x 10^9/L) and elevated white cell counts.

This article discusses the approach to the patient with an elevated white cell count, according to the subpopulation of white cells that is elevated. The best initial strategy includes taking a detailed history and thoroughly examining the patient. Lymphadenopathy and spleen size should be assessed, and a haematologist or other skilled morphologist should examine the blood film.

Neutrophilia

Neutrophilia is by far the most common variation on the elevated white cell theme and has the broadest differential diagnosis. The main questions to answer are whether it is a physiological or pathological response and whether there are other abnormalities.

Physiological or pathological

Infection, physiological stress and trauma are obvious causes of neutrophilia. Cushing's syndrome and corticosteroid therapy are also associated with neutrophilia. Mild leucocytosis (a white cell count of 11 to 15 x 10^9/L) with neutrophilia is common in pregnancy and following splenectomy.

If the count is more extreme than expected in the above disease state (i.e. if the neutrophils (Figure 1) are elevated above 30 x 10^9/L) the possibilities narrow and include:

- a 'leukaemoid response' to infection, inflammation or malignancy (this is a rather confusing term meaning little more than a very elevated white cell count that is not a true leukaemia; usually the cause will be obvious)
- the result of an exogenous granulocyte colony stimulating factor (G-CSF) being given to a patient who is undergoing chemotherapy
- a myeloproliferative disorder (in which case

IN SUMMARY

- **The white blood cell lineage that is most often elevated is the neutrophil; infections, physiological stress and trauma are obvious causes of neutrophilia.**
- **Important causes of lymphocytosis include viral infections, chronic lymphocytic leukaemia and several rare diseases (e.g. hairy cell leukaemia).**
- **In the elderly, asymptomatic monocytosis accompanied by significant neutrophilia is a common presentation of chronic myelomonocytic leukaemia.**
- **Eosinophilia is usually associated with allergic disease or gastrointestinal parasites (e.g. *Strongyloides*).**
- **Basophilia is a rare isolated finding; underlying myeloproliferative disorders are the most common underlying causes of persistent basophilia.**

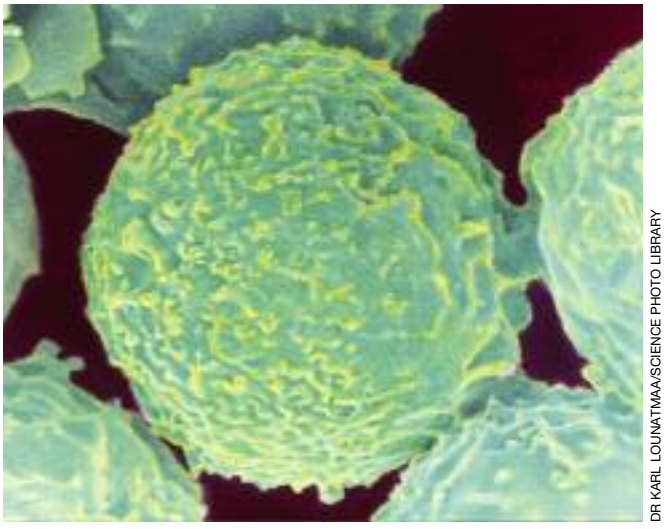

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Figure 1. Neutrophils, the white cell lineage most often elevated. Infection and physiological stress are common causes of neutrophilia.

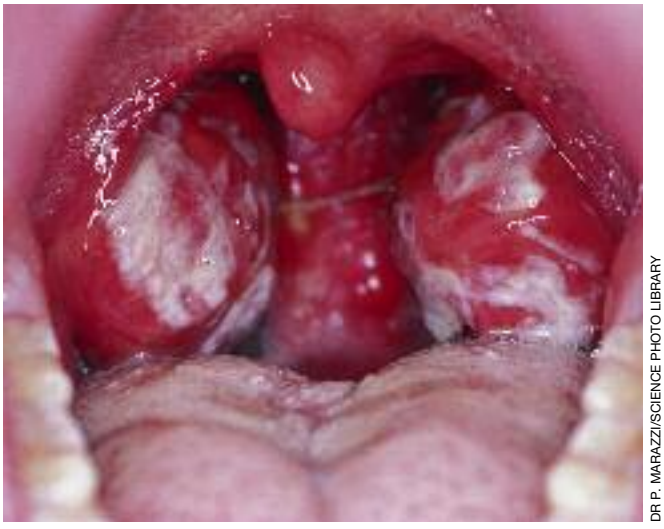

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Figure 2. Infectious mononucleosis is the most common acute viral infection causing lymphocytosis.

other abnormalities will usually be present [see below]).

Most of the above require no further investigation once the underlying cause has been defined. If the white cell count is above 15 x 10^9/L in the absence of an obvious explanation, bone marrow biopsy may be indicated.

Other abnormalities

The association of a moderate neutrophilia and a monocytosis in patients over 50 years of age may indicate chronic myelomonocytic leukaemia, an often indolent disease that is common in this age group.

Thrombocytosis in association with neutrophilia can be seen in patients suffering physiological stress but may also indicate an underlying myeloproliferative disorder (the umbrella term covering chronic myeloid leukaemia, polycythaemia rubra vera, essential thrombocythaemia and myelofibrosis). Splenomegaly on physical examination would strongly support this.

Chronic myeloid leukaemia rarely presents with isolated neutrophilia. Often the white cell count is very high (greater than 100 x 10^9/L) with an obvious 'left shift' (meaning immature myeloid cells such as myelocytes and metamyelocytes being plentiful). Chronic myeloid leukaemia can present with more subtle elevations in the 10 to 20 x 10^9/L range; however, in this case there would often be some other clue, such as basophilia or thrombocytosis. If bone marrow biopsy is performed, it is important to request cytogenetic and molecular studies to detect the characteristic Philadelphia chromosome (i.e. translocation involving chromosomes 9 and 22).

The laboratory may have commented on a 'leucoerythroblastic blood film'. This refers to the presence of immature white cells (metamyelocytes and earlier forms) and nucleated red cells in the blood. This is not uncommonly present in seriously ill patients, but in other contexts it may indicate bone marrow infiltration (for example, carcinoma, myelofibrosis, leukaemia and lymphoma). Bone marrow biopsy is often indicated in this case.

Lymphocytosis

The causes of lymphocytosis include an acute viral infection, chronic lymphocytic leukaemia and several rare diseases.

Acute viral infection

Infectious mononucleosis (Figure 2) is by far the most common acute viral infection causing lymphocytosis. It is usually easily diagnosable in the context of the typical age and clinical syndrome associated with a positive Monospot test with the classical atypical lymphocytes in the blood. Other important viral infections to consider are HIV infection and pertussis.

Table. White cell lineages and major causes of elevation

White cell lineage	Normal range (x 10^9/L)	Important causes of elevations	Comment
Neutrophils	2.0 to 7.5	Infection, stress, myeloproliferative disorders, corticosteroid therapy	Investigate further if significant (e.g. >10 x 10^9/L), persistent, accompanied by immature white cells or other abnormalities and an alternative physiological cause is not apparent
Lymphocytes	1.5 to 4.0	Viral infection, chronic lymphocytic leukaemia (CLL). Asymptomatic lymphocytosis in the elderly is a common presentation of CLL	Most causes can be established on examination of the blood film and, when indicated, by the Monospot test, viral serology and immunophenotype
Monocytes	0.2 to 1.0	Infection, inflammation, malignancy, chronic myelomonocytic leukaemia (CMML)	Asymptomatic monocytosis and neutrophilia in the elderly is a common presentation of CMML
Eosinophils	0.04 to 0.4	Gastrointestinal parasites, allergic dermatoses, asthma, other allergic conditions, very rarely myeloproliferative disorders, carcinomas and Hodgkin's disease	The cause is usually obvious, and it is uncommon for eosinophilia to be the first presentation of underlying malignancy
Basophils	<0.2	Myeloproliferative disorders, systemic mastocytosis	Rarely an isolated finding. Persistent and significant elevation (e.g. >0.4 x 10^9/L) should be further investigated

Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia is common in patients presenting over the age of 50 years with an asymptomatic mild to moderate lymphocytosis. The best diagnostic test for this is flow cytometry, which will demonstrate the characteristic phenotype. Patients with no symptoms, absence of bulky lymphadenopathy and otherwise normal indices, usually require no initial therapy and have a median survival of more than 10 years.

Rare diseases

Rare diseases associated with lymphocytosis are usually flagged by the pathology laboratory and identifiable on flow cytometry. They include hairy cell leukaemia and large granular lymphocytic leukaemia.

Monocytosis

Monocytosis may be seen in the presence of infectious and inflammatory conditions, although this is relatively uncommon as an isolated finding. If the patient is over 50 years of age and the degree of monocytosis is significant (greater than 3 x 10^9/L) and accompanied by significant neutrophilia, chronic myelomonocytic leukaemia is likely. This condition is often indolent and not curable; observation only and supportive therapy when required are usually the best options.

Eosinophilia

Eosinophilia is usually associated with obvious allergic disease. Consider asthma and eczema, and also helminthic infection (in patients who have lived in the tropics, consider strongyloidiasis, which can be a serious infection with subsequent immunosuppression). Most patients with isolated mild eosinophilia do not require further investigation. Eosinophilia may be associated with Hodgkin's disease, carcinoma and myeloproliferative disorders; however, first presentation with isolated eosinophilia is very rare.

Basophilia

Basophilia is rare as an isolated finding. If it is persistent further haematological investigation is indicated, with underlying myeloproliferative disorders being the most common underlying diseases.

Conclusion

The cause of an elevated white cell count may not be obvious. History and examination of the patient and examination of the blood film by a skilled morphologist can resolve most cases. MT