BMJ

BMJ 2014;348:g1721 doi: 10.1136/bmj.g1721 (Published 3 March 2014)

PRACTICE

RATIONAL TESTING

Investigating an incidental finding of lymphopenia

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

A 55 year old man had a full blood count undertaken when he presented with fatigue. There was no significant medical history of note. He was a non-smoker who took no medications. He was noted to have a lymphopenia of 0.8×10^9/L (reference interval 1.5-4.0×10^9/L). Otherwise his results were normal, with haemoglobin of 135 g/L (130-180 g/L), white cell count 4.2×10^9/L (4-12×10^9/L), and platelet count 150×10^9/L (140-400×10^9/L). He did not return for follow-up but presented to a local hospital emergency department six months later with a short history of increasing breathlessness. He was diagnosed with a severe bacterial pneumonia, from which he recovered after prolonged therapy with intravenous antibiotics. His lymphocyte count during admission ranged between 0.5 and 1.0×10^9/L.

What should be the next investigation?

Lymphopenia and its causes

T lymphocytes make up most (60-80%) of the total peripheral lymphocyte count, with the rest comprising B lymphocytes and natural killer cells. These subsets can be quantified by flow cytometry but not from routine full blood count or morphological examination of a blood film. Lymphocyte numbers vary with age; infants normally have higher counts (>2.8×10^9/L when <3 months old) compared with adults, for whom the lower reference limit is usually 1.5×10^9/L.

As the reference interval for the lymphocyte count covers the central 95% of values in a healthy population, 5% of normal individuals will have values outside the reference interval. Lymphopenia is a relatively common laboratory finding and has been documented in 1.5-3% of full blood count samples from both community and hospitalised patients.[1 2] Most lymphopenias result from a reduction in T cell numbers. Chronic severe lymphopenia (<0.5×10^9/L) may predispose patients to opportunistic infections such as pneumocystis pneumonia, oesophageal candidiasis, herpes zoster, and systemic cytomegalovirus.

Lymphopenia may be considered as primary or secondary. Primary causes are uncommon and include a wide range of primary immunodeficiency diseases. These diseases are characterised by recurrent, severe or unusual infections, failure to thrive in children, and sometimes autoimmune and inflammatory complications. Lymphopenia is a feature of many but not all of these disorders. Persistent lymphopenia is a common feature of severe combined immunodeficiency, which typically presents with severe, recurrent infections and failure to thrive in the first year of life[3] and usually requires stem cell transplantation. Thus persistent lymphopenia in an infant should be followed up.[4] Other primary immunodeficiencies such as common variable immune deficiency present later in life (older children and adults) with recurrent bacterial infections, especially of the respiratory tract, panhypogammaglobulinaemia, and varying degrees of lymphopenia. Although the main focus of this article is on adults with secondary or acquired causes of lymphopenia, it is worth considering primary immune deficiency in individuals with relevant clinical features such as problematic infections, failure to thrive, and positive family history.

Secondary lymphopenia is common and can result from reduced lymphocyte production, increased lymphocyte destruction, or altered partitioning of lymphocytes between the blood and different lymphoid tissues. It may be due to several causes, the commonest of which are listed in box 1, and is usually reversible. It is often seen in acutely unwell patients; in a case series of over 1000 hospital patients, bacterial or fungal sepsis was the commonest cause (24%) of a lymphocyte count of <0.6×10^9L, followed by recent surgery (22%), malignancy (17%), and corticosteroid treatment (15%).[2] A low count persisted beyond six months in only 6% of subsequent analyses.[2]

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Learning points

- Lymphopenia is a common finding from a full blood count, especially in elderly patients, where it is usually of no clinical significance. No further investigation is advised in an elderly patient with a lymphocyte count >0.5×10^9/L in the absence of any concerning symptoms
- Most cases are reversible and do not require specialist evaluation. The lymphopenia may reflect a response to stress such as acute infection or recent surgery or be iatrogenic secondary to medication, especially immunosuppressant drugs such as steroids
- Symptomatic patients with persistent lymphopenia should be referred to the most appropriate specialty based on clinical and laboratory features
- In those with unexplained moderate to severe lymphopenia (lymphocyte count <1×10^9/L) offer HIV testing
- Persistent lymphopenia that remains stable over a six month period and in the absence of symptoms, clinical findings, or abnormal results from investigations does not require further investigation

Lymphopenia is extremely common in viral illnesses; 68% of adult patients and 92% of paediatric patients had reduced lymphocyte counts during the 2009 influenza A pandemic.[5] It is also common in HIV infected individuals, and it is important to consider HIV infection in anyone with chronic moderate to severe lymphopenia.[6 7]

Assessment in primary care

Elderly patients have a tendency to lymphopenia,[8] and if the lymphocyte count is >0.5×10^9/L in the absence of other concerning symptoms no further investigation is required. In younger adults with persistent unexplained moderate to severe lymphopenia (lymphocyte count <1×10^9/L) consider:

- Has the patient had a recent (within the past six months) infection (viral, bacterial, or other as listed in box 1) to account for the lymphopenia?
- Is there a history of infections which may suggest underlying immune deficiency (such as pneumocystis, severe warts, long history of recurrent infections)?
- Is the patient taking any medication that may cause lymphopenia (such as immunosuppressive agents, chemotherapy)?
- Is there any underlying evidence of systemic disease that may be associated with lymphopenia (such as autoimmune disorders, lymphoma, other malignancies, sarcoidosis, renal or cardiac failure)?
- Does the patient have any symptoms that may suggest an underlying lymphoma (such as weight loss, fever, or night sweats)?
- Is the patient malnourished?
- Is there any history of alcohol misuse?
- Are there abnormal findings on examination (such as lymphadenopathy, splenomegaly, joint abnormalities, skin rashes)?

Suggested investigations

- Repeat full blood count and blood film after six weeks to confirm lymphopenia
- Urea and electrolytes to assess renal function; liver function tests
- HIV antibody test—Consider this in patients with high risk activities or chronic severe unexplained lymphopenia
- Antinuclear antibody screen and rheumatoid factor test if a connective tissue disorder is suspected
- Serum immunoglobulins—A global reduction of immunoglobulins (hypogammaglobulinaemia) or reduction of a specific isotype (such as IgG, IgA, IgM) may be seen in patients with primary immunodeficiency. Lymphoproliferative disorders can also be associated with reduction of immunoglobulin levels.

The next step

Refer a patient with symptoms of a serious infection or possible malignancy or systemic disorder to the most appropriate specialty on the basis of clinical and laboratory features. In an otherwise well patient with isolated lymphopenia, normal physical findings and negative investigations, we suggest a repeat full blood count at six months. If there is no change in blood count and the patient remains well there is no need to investigate further.

Outcome

This patient was found to be infected with HIV. His CD4 count was low at 280×10^6/L, and he was referred to the infectious diseases team for antiretroviral therapy. On further questioning, he gave a history of high risk sexual activity while on a business trip to South Africa three years previously.

Lymphopenia is common, usually associated with acute illness and usually reversible. If moderate to severe lymphopenia (lymphocyte count <1×10^9/L) persists without an obvious trigger such as medication or underlying autoimmune or inflammatory disorders, then further investigation should be considered. It is important to consider HIV infection in anyone with chronic moderate to severe lymphopenia: 53% of individuals with a new diagnosis of HIV infection had a lymphocyte count <1.5×10^9/L.[9] Despite the available guidance and accessibility of HIV testing, this is often overlooked.[6 7]

Competing interests: We have read and understood the BMJ Group policy on declaration of interests and have no relevant interests to declare.

Patient consent not required (patient anonymised, dead, or hypothetical).

Provenance and peer review: Commissioned; externally peer reviewed.

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Box 1: Common causes of lymphopenia

- Infection
  Viral (including HIV, influenza, hepatitis)
  Bacterial (including tuberculosis)
  Parasitic (including malaria)
  Fungal (including histoplasmosis)
- Medication
  Immunosuppressive agents (such as corticosteroids, methotrexate, azathioprine)
  Monoclonal antibody therapies (such as rituximab)
  Chemotherapy (such as fludarabine, cladribine)
- Systemic disorders
  Autoimmune diseases (such as rheumatoid arthritis, systemic lupus erythematosus)
  Inflammatory bowel disease
  Renal failure
  Cardiac failure
  Sarcoidosis
- Malignancy
  Lymphoproliferative disorders
  Solid organ malignancies
- Severe malnutrition
- Alcohol abuse
- Radiotherapy
- Recent surgery

Cite this as: *BMJ* 2014;348:g1721