Assessing lymphadenopathy in adults
a systematic approach

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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Lymphadenopathy is a common presenting problem and may be challenging to both general practitioners and specialists. This article gives simple and practical guidelines for assessing adults with lymphadenopathy, focusing on the relevant investigations.

Using a systematic approach, the history and examination of the patient with lymphadenopathy will often suggest the diagnosis. Some cases will require more specific investigations, including detailed imaging and lymph node biopsy with specialist referral.

Most lymphadenopathy seen in general practice is benign and commonly related to infections. Only about 1% of presenting patients will have an underlying malignancy (Figure 1).

Lymphadenopathy may be generalised or localised and can be classified as either primary or secondary. A simple classification according to the underlying pathology is a useful guide when investigating its causes (Table 1) .

History

The relevant points of the history are summarised in Table 2. The demographics of a patient – age, sex, race, occupation and habits (e.g. smoking and sexual behaviour) – may be significant. The history should include onset, duration and rate of progression of the lymphadenopathy. Occasionally, lymphadenopathy will be an incidental finding at a routine examination. Specific symptoms should be sought, aiming at likely causes such as infections. For example, the presence of symptoms related to the oropharynx may explain cervical lymphadenopathy.

A prior history of malignancy may be significant. For instance, axillary lymphadenopathy in a patient with a history of breast carcinoma or the removal of a pigmented skin lesion from the torso may indicate metastatic disease. Systemic symptoms such as night sweats, fevers and unexplained weight loss should also be sought. The patient should be asked about symptoms of bone marrow

IN SUMMARY

- **Most lymphadenopathy is benign. In the primary care setting, only 1% of patients have an underlying malignancy.**
- **A full history and examination supplemented by simple initial investigations and/or a period of observation may be sufficient in many cases.**
- **A lymph node biopsy is indicated if lymphadenopathy is persistent and has features suggestive of malignancy, such as firmness, hardness or fixation to underlying structures, or if it is associated with systemic symptoms.**
- **An excision biopsy of the lymph node will give the best chance of the precise diagnosis. However, a core biopsy or fine needle aspiration biopsy are alternatives if excision biopsy is unacceptably invasive.**

Table 1. Causes of lymphadenopathy

- Infections
  - Viral
  - Bacterial
  - Mycobacterial
  - Fungal
  - Protozoal
- Malignancies
  - Primary, e.g. lymphoma, leukaemia
  - Secondary, e.g. breast, melanoma or lung metastases
- Infiltrative diseases, e.g. sarcoidosis
- Autoimmune diseases, e.g. systemic lupus erythematosus, rheumatoid arthritis
- Drug side effects, e.g. pseudolymphoma caused by phenytoin or cyclosporin A

failure or involvement, such as fatigue, recent or recurrent infections and bleeding or bruising. It is also important to ask about travel and pets, which can sometimes give clues to infective causes of lymphadenopathy.

Examination

The 'over the desk' assessment often provides useful information. Does the patient look well or unwell, cachetic or toxic?

Initial assessment of the mass should be directed at ascertaining whether it is truly a lymph node or nodes and excluding, as much as possible, other round masses. Note the lymph node characteristics, such as firmness and possible fixation to adjacent structures. Local draining sites such as the oropharynx or skin should be examined, as should other lymph node regions.

A full physical examination should be performed (Table 3), concentrating on relevant aspects such as the presence of an enlarged liver or spleen, or other abdominal masses including intra-abdominal lymph nodes. Signs of bone marrow failure (e.g. anaemia and bruising) should also be sought.

Investigations

The need for investigations is guided by the history and examination. Investigations that may

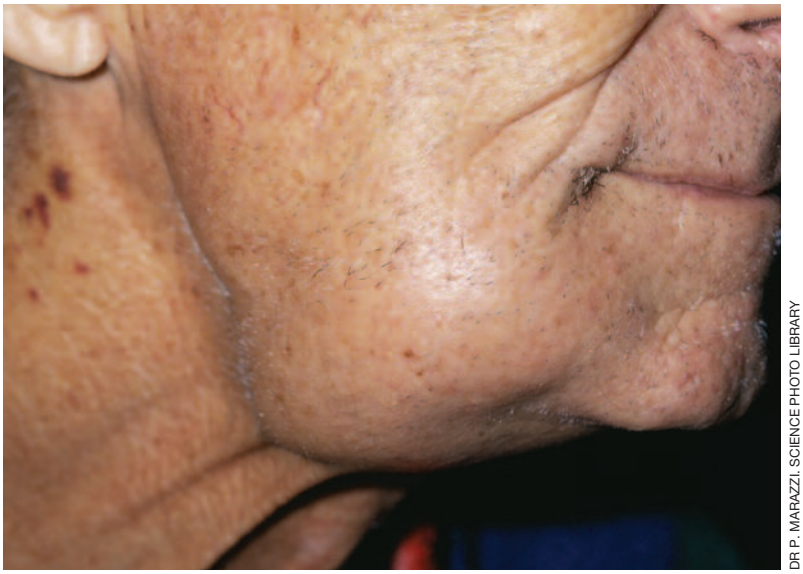

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Figure 1. Non-Hodgkin's lymphoma. Only about 1% of patients presenting with lymphadenopathy will have an underlying malignancy.

Table 2. History

- Basic demographics: age, sex, race, habits (e.g. sexual, smoking), occupation
- Features of lymphadenopathy: onset, rate of progression, pain or other symptoms
- Asymptomatic or incidental finding
- Systemic symptoms: unexplained weight loss, drenching night sweats
- Past history: previous malignancy, other significant medical history
- Current medications
- Other: travel, pets

Table 3. Examination

- Vital signs: temperature, pulse and blood pressure
- Local nodes: site, size, number, firmness, mobility
- Other clinically assessable lymph glands
- Abdomen: presence of enlarged liver, spleen or masses
- Local lesions on the skin or oropharynx
- Other relevant systems

Potential initial investigations for lymphadenopathy

Not all patients with lymphadenopathy will require all the following investigations. The history and examination determine those that are appropriate.

- Full blood count, including blood film and differential values.
- Electrolytes, urea and creatinine, lactate dehydrogenase, calcium and uric acid levels and liver function tests.
- Erythrocyte sedimentation rate and C-reactive protein level.
- Serological studies: may include tests for Epstein-Barr virus, cytomegalovirus, HIV and human T cell lymphotrophic virus infections, toxoplasmosis, cryptococcosis and cat scratch disease.
- Sputum microbiology (e.g. culture and Ziel-Nielsen stain/PCR for mycobacteria) and cytology.
- Autoimmune screen: antinuclear antibody, anti-dsDNA, rheumatoid factor and complement levels.
- Radiology: chest x-ray, ultrasound, CT or MRI.

be useful are shown in the box on this page.

Initially no specific investigations may be indicated. Small soft upper cervical nodes following a well characterised upper respiratory tract infection are likely to be reactive and the patient may be simply observed and monitored for regression (or progression), usually over a few weeks.

Serology

If glandular fever (infectious mononucleosis) is suspected, a monospot and specific Epstein–Barr virus serology is indicated.

Cytomegalovirus, HIV-1 and -2 and toxoplasmosis can all cause a glandular fever-like syndrome, and serology to exclude these infections may also be indicated.

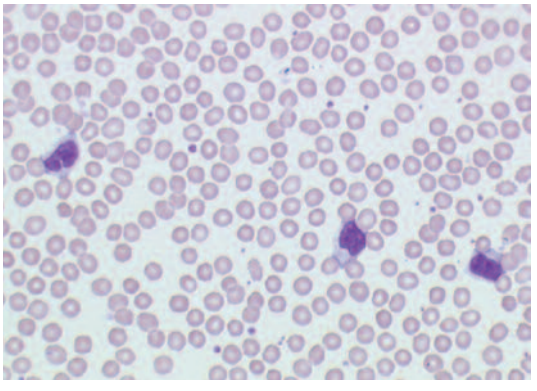
Haematology

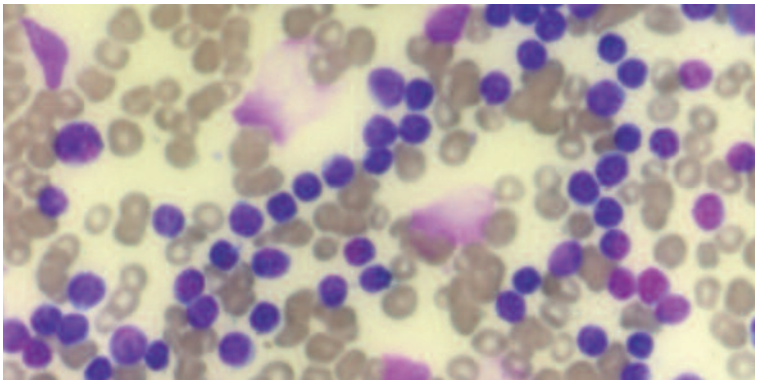
In classic glandular fever, a blood film may display the characteristic features of numerous atypical lymphocytes (Figure 2a), while occasionally other features such as thrombocytopenia may be present.

The full blood count may also point to the diagnosis of other common causes of lymphadenopathy. The most common type of leukaemia, chronic lymphocytic leukaemia, frequently presents with generalised lymphadenopathy. It has a typical blood film appearance with smudge or smear cells (Figure 2b) as well as a virtually diagnostic immunophenotype (co-expression of T-lymphocyte marker CD5 on the leukaemic B-lymphocytes, which express CD19 and CD20). This can be demonstrated readily by flow cytometric immuno - typing of peripheral blood lymphocytes. This combination of peripheral blood features and immunophenotype is so typical that many haematologists would consider a formal node biopsy or even a bone marrow biopsy unnecessary to confirm the diagnosis, at least in the initial assessment.

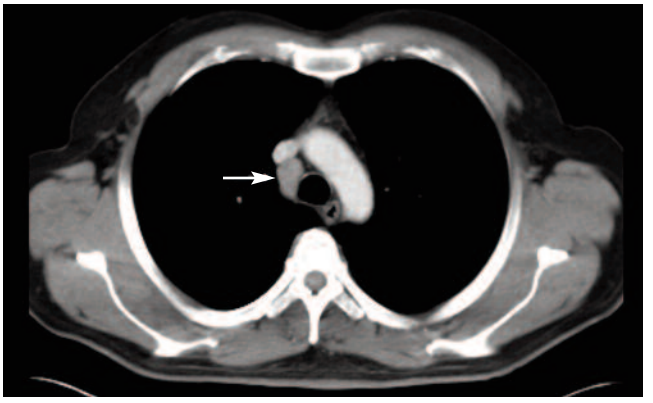
Biochemical markers

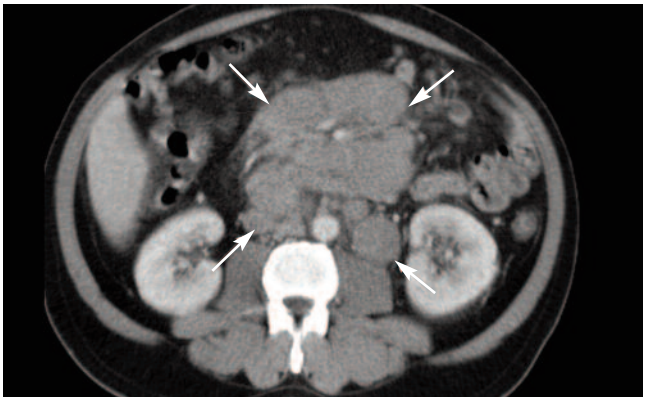
Other relevant initial investigations may include measurement of electrolytes, urea and creatinine, calcium, uric acid and lactate dehydrogenase (LDH) levels and liver function tests. A high LDH level or hypercalcaemia may point to underlying malignancy. Inflammatory markers such as the erythrocyte sedimentation rate and C-reactive protein may be useful, but they are essentially nonspecific.





Figures 2a and b. Typical blood films from patients presenting with lymphadenopathy. a (left). Atypical lymphocytes classically seen in glandular fever (infectious mononucleosis) induced by Epstein–Barr virus. The atypical mononuclear cells are activated T-lymphocytes reacting against the virally infected B-lymphocytes. b (right). Blood film from a patient with chronic lymphocytic leukaemia. The peripheral white cell count was 180 x 10^9/L with 90% lymphocytes and smudge or smear cells. The leukaemic cells express B-lineage lymphocyte markers such as CD19 and CD20 and aberrantly co-express the T-lymphocyte marker CD5.





Figures 3a and b. CT images of patients with lymphadenopathy. a (left). CT scan of the thorax demonstrating paratracheal lymphadenopathy (arrow) in a patient with Hodgkin's disease. b (right). CT scan of the abdomen demonstrating retroperitoneal and mesenteric lymphadenopathy (arrows) in a patient with newly diagnosed sarcoidosis.

Microbiology and immunology

Other potentially relevant investigations in selected patients include specific microbiological cultures (wound or throat swabs) and a screen for possible autoimmune disease by detection of autoantibodies such as antinuclear antibodies, anti-dsDNA and rheumatoid factor, and complement levels.

Radiology

Appropriate radiology may include a chest x-ray to search for signs of infection or mediastinal or hilar lymphadenopathy. Abdominal imaging (ultrasound, CT scan; Figures 3a and b) may be used to investigate a palpable intra-abdominal mass or to define hepatosplenomegaly. Sophisticated radiological investigations such as a CT scan or MRI, preferably with oral and intravenous contrast, may be indicated to define abnormalities seen on screening tests, such as chest x-ray or ultrasound. Extensive whole body radiology or scanning is rarely indicated at first presentation.

Lymph node biopsy

Most unexplained significant and/or persistent lymphadenopathy warrants biopsy. Excision biopsy of the lymph node has the highest chance of providing the diagnosis, as it enables the most accurate assessment of lymph node architecture and provides adequate material for additional tests.

Fine needle aspiration biopsy (FNAB) and/or a core biopsy are, in general, less invasive and can frequently be performed in an ambulatory setting. They are potential alternatives to excision biopsy – at least for the initial assessment for intra-abdominal or intrathoracic lymphadenopathy where an excision biopsy may be unacceptably invasive.

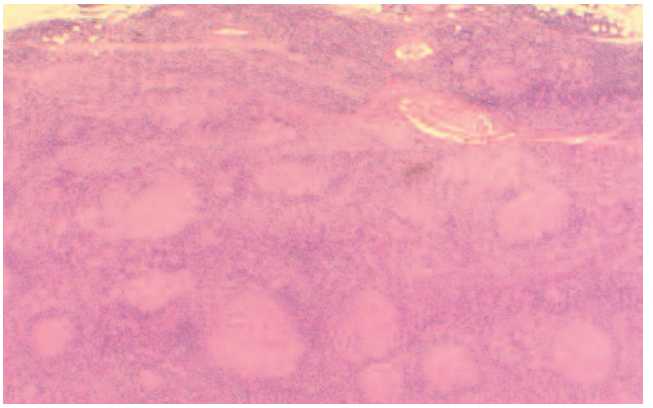


Figure 4. An excision lymph node biopsy specimen demonstrating the typical appearance of follicular non-Hodgkin's lymphoma. The malignant follicles efface the normal nodal architecture in this low-grade non-Hodgkin's lymphoma.

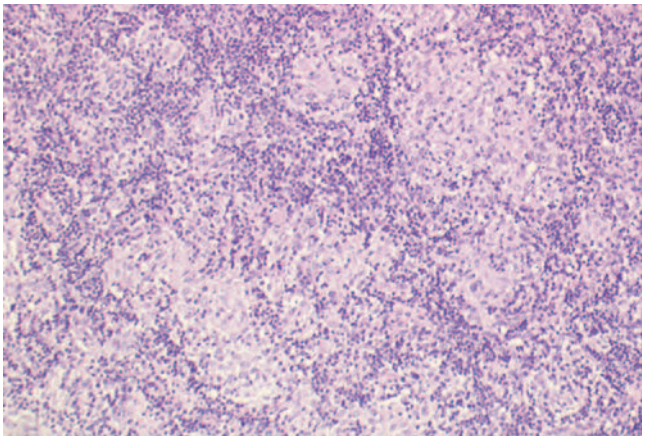


Figure 5. Sarcoidosis. Classic noncaseating granulomas from a core biopsy from a patient with systemic symptoms and intra-abdominal lymphadenopathy.

However, there is a well recognised false negative rate with FNAB and because nodal architecture is not preserved, the precise diagnosis may not be made. For instance, to subclassify some non-Hodgkin's lymphomas, nodal architecture is crucial. Also, the fibrotic node in nodular sclerosing Hodgkin's disease may preclude aspiration of diagnostic material with FNAB.

Such issues are of less concern if a core biopsy can be obtained and additional investigations such as immunophenotyping, cytogenetics and molecular studies can be performed. These latter investigations are often now considered integral to the assessment of many causes of lymphadenopathy.

Lymphoproliferative disorders, such as hairy cell leukaemia and Burkitt's lymphoma, have typical immunophenotypic patterns that, in conjunction with classical histological appearances, are integral to reaching the precise diagnosis. Similarly, cytogenetic and molecular genetic analyses are increasingly important in the definitive diagnosis and monitoring of specific malignancies. As an example, the most common low grade non-Hodgkin's lymphoma (which accounts for more than 80% of cases), follicular lymphoma (Figure 4), is characterised by a recurrent cytogenetic translocation (t[14;18]) that causes a molecular abnormality (bcl 2/ Ig H fusion gene).

Microbiological assessment of the biopsy specimen, including formal culture, should always be considered if there is a suspicion that the lymphadenopathy is a manifestation of an infection. Special tests for the detection of potential pathogens, for example immunofluorescence for viruses such as cytomegalovirus, may also be relevant. When microscopy with appropriate staining and cultures are negative for mycobacteria, but there is strong clinical suspicion, PCR can be used as a more sensitive method of detection.

Hence, the clinical scenario (infection versus malignancy) and initial tests can help to determine the need for more complex and sophisticated investigations. However, the decision as to which additional investigations are required may occasionally depend on the initial assessment of a biopsy by an anatomical pathologist experienced in lymph node pathology.

Investigations after diagnosis

Additional investigations are often needed after a diagnosis has been made. For example:

- formal respiratory assessment in

patients with sarcoidosis (Figure 5)
- detailed staging of a patient with newly diagnosed lymphoma, using CT gallium or PET scans and bone marrow biopsy.

Conclusion

Lymphadenopathy is a common presentation that, although frequently benign, can be the marker of a potentially serious but often treatable underlying condition. Assessment and investigation of patients should follow a logical and ordered progression, modified specifically for the clinical situation. If biopsy is indicated, every effort should be made, as far as practical, to obtain the best possible tissue for histopathology and other additional tests to ensure the most precise diagnosis. Once a definitive diagnosis has been made, supplemental investigations are often indicated. MT

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Further reading

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