MedicineToday 2012; 13(5): 18-24

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CLINICAL INVESTIGATIONS FROM THE RACP

# Investigating cervical lymphadenopathy

## Don't miss the serious and malignant conditions

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## Key points

- There is no substitute for a thorough history and physical examination.
- Most cases of cervical lymphadenopathy are benign or self-limiting.
- Patients should be referred early if there is a high clinical suspicion of malignancy.
- In cases of persistent unexplained lymphadenopathy, tissue diagnosis is the key.
- The empirical treatment of patients with persistent unexplained lymphadenopathy with antibiotics or corticosteroids should be avoided.

**In this series, we present authoritative advice on the investigation of a common clinical problem, especially commissioned for family doctors and written by members of the Royal Australasian College of Physicians.**

Cervical lymphadenopathy is a common presentation in primary care. Although most cases are benign or self-limiting,[1-3] the challenge for clinicians is to identify those cases that represent malignancy or other potential serious conditions. The following article will outline a diagnostic approach to this problem.

Normal cervical lymph nodes are generally less than 1 cm in diameter. Lymphatic groups and their drainage are shown in Figure 1.

### HISTORY AND PHYSICAL EXAMINATION

Most of the clues for the diagnosis of cervical lymphadenopathy can be found in a thorough and focused history and physical examination.

Lymphadenopathy that arises acutely and lasts for less than two weeks is unlikely to be malignant. The same applies to lymphadenopathy that has been present for more than a year with no increase in size, especially if the lymph node is less than 1 cm in diameter.[4] The likelihood of malignancy increases with advancing age of the patient.[5]

History should focus on potential causes of lymphadenopathy (Table 1), including exposure to infectious contacts, medication use, travel history, exposure to pets and high-risk behaviours (e.g. intravenous drug use, risky sexual behaviours). Symptoms of infection include fevers, pharyngitis, conjunctivitis, skin ulceration and localised tenderness. If there is a history of heavy smoking and drinking, metastatic lymphadenopathy from a carcinoma of the aerodigestive tract needs

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to be carefully considered. Constitutional symptoms such as drenching night sweats and significant unintentional weight loss (greater than 10% of body weight over a six-month period) are nonspecific, but raise concern for the presence of an underlying malignancy or chronic infection such as tuberculosis. In patients with autoimmune conditions, it is unusual for localised or generalised lymphadenopathy to be present in the absence of active disease. The patient may have noticed sore, stiff or swollen joints or a skin rash.

A careful examination of the cervical lymph nodes, taking into account the features listed in Table 2, provides important clues to the diagnosis. Examination of the other lymph node groups (supraclavicular, axillary, epitrochlear, inguinal), as well as an abdominal examination for the presence of hepatomegaly or splenomegaly, should be performed as part of the routine examination in all patients who present with lymphadenopathy. The presence of these features indicates a systemic disease process.


In patients with isolated cervical lymphadenopathy, examination of the drainage areas of the affected node(s) for lesions may reveal a particular infective or malignant aetiology. For example, in the older patient with a history of smoking or high alcohol intake, the presence of cervical lymph nodes that are

**TABLE 1. AETIOLOGY OF LYMPHADENOPATHY**

| Cause | Localised cervical lymphadenopathy | Generalised lymphadenopathy* |
|---|---|---|
| **Infective** | • Bacterial adenitis (*Staphylococcus, Streptococcus*)<br>• Tuberculous lymphadenitis<br>• Oropharyngeal infections<br>• Dental infections<br>• Skin conditions – e.g. eczema, acne | • Viral – e.g. Epstein–Barr virus, HIV, cytomegalovirus |
| **Neoplastic** | **Solid organ**<br>• Head and neck cancer metastases – oropharynx, nasopharynx, laryngeal, thyroid<br>• Oesophageal | **Haematological**<br>• Lymphoma<br>• Non-Hodgkin lymphoma<br>• Hodgkin lymphoma<br>• Leukaemias<br>• Chronic lymphocytic leukaemia<br>• Acute leukaemias (rare) |
| **Medications** | | • e.g. phenytoin, carbamazepine, allopurinol (rare) |
| **Other** | • Cervical subacute necrotising lymphadenitis (Kikuchi Fujimoto disease)† | • Systemic lupus erythematosis<br>• Sarcoidosis |

* Most of these conditions may also present as localised lymphadenopathy.
† Cervical subacute necrotising lymphadenitis (Kikuchi Fujimoto disease) is an uncommon cause of cervical lymphadenopathy.[6] It is more prevalent in Asian populations and is rarely described in Western populations. It is a benign and self-limiting syndrome characterised by tender cervical (usually posterior triangle) lymphadenopathy, fevers and night sweats. Between 30 and 50% of cases may have associated splenomegaly, weight loss and rash. Diagnosis is made by excision biopsy.

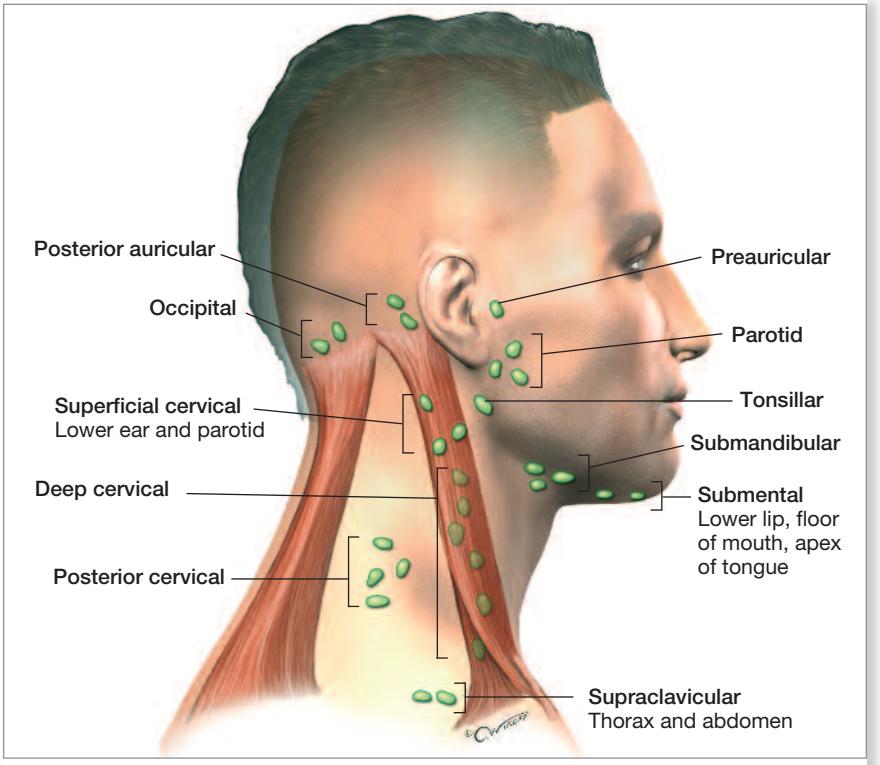





Figure 1. Lymphatic groups and their drainage.

asymmetrical, fixed, firm and matted is suggestive of a metastatic solid organ malignancy arising from the oropharynx. Associated symptoms may include a hoarse voice or sore tongue. These findings should prompt an examination of the oropharynx and referral of the patient to a specialist.

An enlarged supraclavicular lymph node is highly suggestive of malignancy. Right-sided supraclavicular lymphadenopathy is associated with cancer in the mediastinum, lungs or oesophagus. Left-sided supraclavicular lymphadenopathy (Virchow's node) is associated with intra-abdominal malignancy (e.g. of the stomach, pancreas or ovaries).

In patients with haematological malignancies, the lymph nodes tend to be asymmetrical and of a more rubbery consistency, and they may or may not be fixed. Lymphadenopathy related to infectious aetiologies may be symmetrical and tender. However, the presence or absence of pain is not reliable for differentiating malignancy from benign aetiologies.

**TABLE 2. FEATURES SEEN ON LYMPH NODE EXAMINATION**

| Nodal characteristic | Feature on examination |
|---|---|
| Site | Pathology in nodal drainage area; unilateral or bilateral |
| Size | Less than 1 cm is normal |
| Shape | Regular or irregular |
| Skin | Overlying skin erythematous in acute inflammation |
| Consistency | Firm, craggy, rubbery, soft or fluctuant |

**SUSPICIOUS FEATURES OR 'RED FLAGS' OF MALIGNANCY**

- Lymphadenopathy persisting for more than four weeks
- Patient older than 50 years
- Unilateral or supraclavicular lymph node affected
- More than 10% weight loss in the past six months
- Night sweats ('Do you have to change the sheets or your night clothes?')
- Nodal character – fixed, hard and matted

## WHAT INVESTIGATIONS SHOULD BE ORDERED?

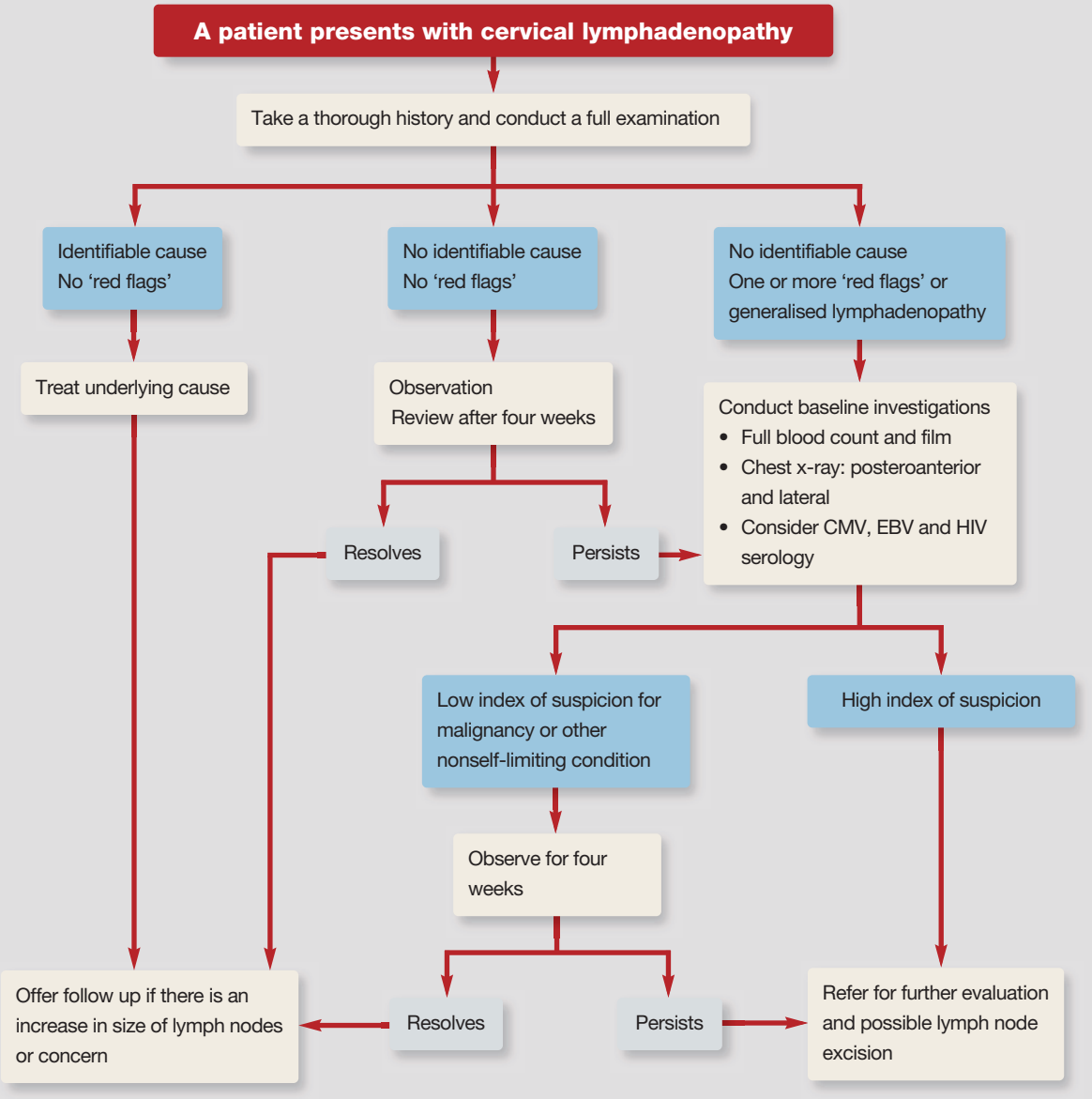
The gold standard investigation of patients with cervical lymphadenopathy is an excision biopsy of the largest involved node. However, because most causes of cervical lymphadenopathy are self-limiting, this is not appropriate in most cases. The diagnostic algorithm on page 21 outlines an approach to selecting patients in whom further investigation is warranted.

It is reasonable to observe patients with isolated small cervical lymphadenopathy with no suspicious features (see the box on this page) for four weeks. However, should symptoms evolve, the patient should be evaluated sooner. The presence of generalised lymphadenopathy is indicative of a systemic process and baseline investigations should be performed in all such cases.

### Blood tests

A full blood count and film in the first instance can be useful in identifying infective and haematological conditions. A peripheral blood lymphocytosis may be

## A DIAGNOSTIC ALGORITHM FOR PATIENTS WITH CERVICAL LYMPHADENOPATHY




ABBREVIATIONS: CMV = cytomegalovirus; EBV = Epstein–Barr virus; HIV = human immunodeficiency virus.

seen. On blood film examination, atypical lymphocytes (Figure 2) can be seen in viral infections such as Epstein–Barr virus (EBV) infection. Atypical lymphocytes are not specific and can be seen in many viral infections, including HIV infection. The presence of atypical lymphocytes should prompt further investigation for EBV heterophile antibodies (using a monospot test) with or without EBV serology. Testing for HIV should also be considered. A positive monospot test does not preclude the presence of acute HIV infection.

Chronic lymphocytic leukaemia often presents with localised or generalised lymphadenopathy associated with peripheral blood lymphocytosis and 'smudge cells' identified on blood smear (Figure 3). If there is a persistent lymphocytosis and suspicious morphological features

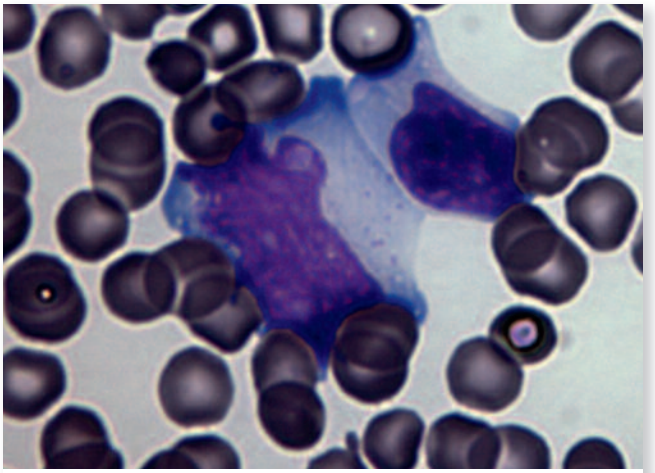


Figure 2. Peripheral blood film showing atypical lymphocytes. These may be seen in viral infections such as Epstein–Barr virus, cytomegalovirus and HIV infections. They are typically pleomorphic, with plentiful basophilic cytoplasm and 'scalloped edges'.

on blood smear, peripheral blood immunophenotyping by flow cytometry with T- and B-cell subsets should be ordered and the patient referred to a haematologist.

### Imaging

In a patient with persistent cervical lymphadenopathy, a chest x-ray should be performed as a screening investigation. The presence of hilar lymphadenopathy raises the suspicion of the presence of tuberculosis, sarcoidosis or Hodgkin lymphoma

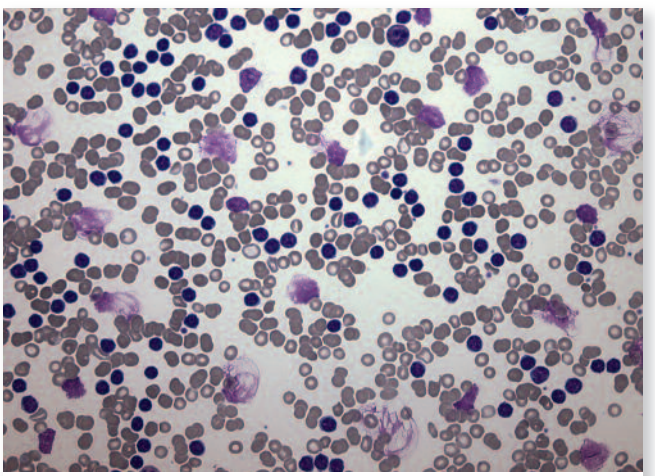


Figure 3. Peripheral blood film from a patient with chronic lymphocytic leukaemia showing the typical morphological features of mature lymphocytes and 'smudge' cells.

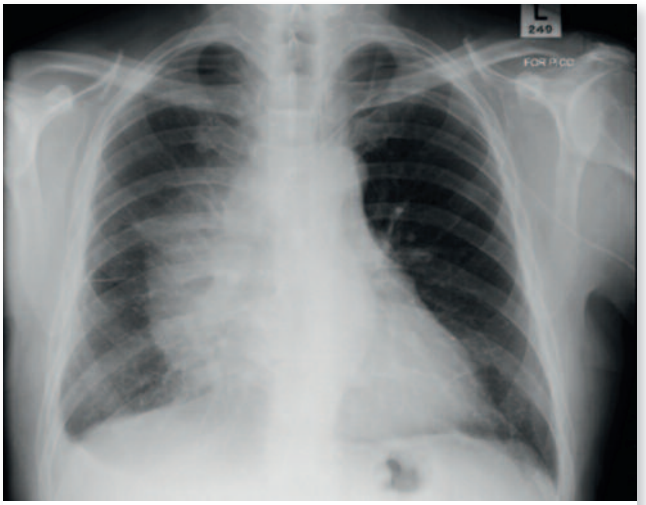


Figure 4. Chest x-ray showing a widened mediastinum that is hilar plus mediastinal lymphadenopathy secondary to Hodgkin lymphoma.

(Figure 4). In contrast, parenchymal lung masses suggest a potential solid organ primary or metastatic malignancy.

All patients with an identified chest x-ray abnormality will require referral to the appropriate specialist for further investigation.

Further imaging investigation with ultrasound or CT scanning may occasionally be useful in differentiating lymph nodes from other structures, for staging or for defining lymph nodes more accurately to guide biopsy. However, further imaging adds little to actually making the diagnosis. If there is high clinical suspicion of a malignancy, the performance of these investigations should not delay surgical referral. In the assessment of a patient with cervical lymphadenopathy, an ultrasound usually adds little additional information that is not provided by a thorough physical examination, and is not routinely encouraged.

## Biopsies

There are several ways in which a lymph node can be biopsied.

A fine-needle aspirate is relatively noninvasive and more easily performed than other biopsies. With correct lymph node selection, sometimes with the aid of ultrasound, it is useful to identify the involvement of lymph nodes with solid organ carcinomas. However, in most cases, a fine-needle aspirate alone is insufficient to make an accurate diagnosis of lymphoma because it provides no information about nodal architecture and has a significant false-negative rate due to sampling error. It may be appropriate in the setting of a suspected relapse in a patient with a prior history of lymphoma.

An excision biopsy is the gold standard because it allows cytology, microbiology, nodal architecture (essential for the diagnosis of a haematological malignancy) and immunohistochemistry to be examined and assessed. This is the preferred investigation if a haematological malignancy is suspected. The test is invasive and not all lymph nodes are amenable to excision.

Although Australia has one of the lowest incidence rates of tuberculosis worldwide at 6.2 per 100,000 population,[7] the incidence in people undergoing pre-migration screening is considerably higher at 137 per 100,000 population.[8] As there is no definitive way of differentiating tuberculous lymphadenitis from other aetiologies, including lymphoma, without biopsy and culture, clinicians should have a high index of suspicion of tuberculosis in patients who have arrived in Australia from endemic areas such as South East Asia and the Asian Subcontinent. Tests such as the Mantoux test are not helpful in patients who are likely to have had previous exposure because they do not differentiate between past and active tuberculosis infection.

A core biopsy is a compromise to an excision biopsy in patients in whom a lymphoma is suspected. However, it is only appropriate when a lymph node is not readily accessible for an excision biopsy.

## EMPIRICAL THERAPY

Empirical treatment of persistent unexplained lymphadenopathy with either antibiotics or corticosteroids is not indicated. This may mask the cause and prevent a diagnosis.

## WHEN TO REFER

After the performance of the basic investigations described above it is appropriate to seek specialist advice or referral before proceeding with further investigations such as biopsies. When the clinician is highly suspicious of a nonself-limiting condition such as lymphoma, prompt referral of the patient is encouraged.

## CONCLUSION

In cases of persistent unexplained cervical lymphadenopathy, tissue pathology remains the key. With the aid of a thorough clinical history and physical examination, the clinician will be able to appropriately select the patients who require further invasive investigation. MT

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COMPETING INTERESTS: None.