Lymphadenopathy

Lymphadenopathy may present at isolated or generalized sites and has a wide range of causes. A careful and thorough approach is essential in evaluating this commonly encountered finding. In addition, these types of cases often lend themselves well to the assessment of focused history taking and examination in PACES or the MRCS exams. This article will review common causes of lymphadenopathy and provide a practical approach to the assessment and investigation of this condition.

Introduction

Lymphadenopathy is a common presenting sign to primary care physicians and many cases are self-limiting. However, when referred to secondary care, cases of lymphadenopathy are normally in the context of persistent lymphadenopathy or lymphadenopathy associated with systemic symptoms. The National Institute for Health and Clinical Excellence (2011) has published guidelines on referral for suspected cancer. This article summarizes the causes of lymphadenopathy, discusses key considerations in the history and examination that help distinguish between benign and malignant causes and finally discusses further investigations including obtaining diagnostic biopsies.

Overview

Lymphadenopathy is the presence of lymph nodes that are abnormal in size, consistency or number (Dotan and Bromberg, 2011) and may be categorized as localized, regional or generalized. Localized lymphadenopathy is usually caused by infection or malignancy draining to an adjacent lymph node group. Regional lymphadenopathy affects multiple contiguous nodal regions as occurs in classical Hodgkin's lymphoma, whereas generalized lymphadenopathy affects multiple lymph node sites above and below the diaphragm. The causes are varied (*Table 1*).

A lymph node that is >1 cm should be considered pathological with the exception of inguinal lymph nodes, which may be considered normal when <2 cm. Tonsillitis (viral or bacterial) is frequently accompanied by painful enlargement of the jugulodigastric lymph nodes in the neck and is a good example of local infection leading to enlargement of lymph nodes draining a site of infection. Patients with widespread skin disorders often have generalized, usually relatively small volume, lymph node enlargement, so-called dermatopathic lymphadenopathy. This rarely affects deep nodal groups such as the retroperitonium, pelvis, abdomen or mediastinum. Occasionally, tattoo ink is visible in the biopsy specimen (*Figure 1*).

The 'well' patient with a persistent or enlarging lymph node is of concern as this is not an uncommon presentation of malignancy. Virchow's node, known to every medical student (the presence of an enlarged lymph node in the left supraclavicular fossa – Troisier's sign), is said to be highly suspicious of gastric carcinoma although other malignancies, particularly lymphoma, may present this way. In adult patients simple inspection of the peripheral blood count is important. Chronic lymphocytic leukaemia is often accompanied by lymphadenopathy and a lymphocytosis. In this situation flow cytometry can be used to identify a clonal popula-

Figure 1. Histological section of dermatopathic lymphadenopathy with visible tattoo ink.

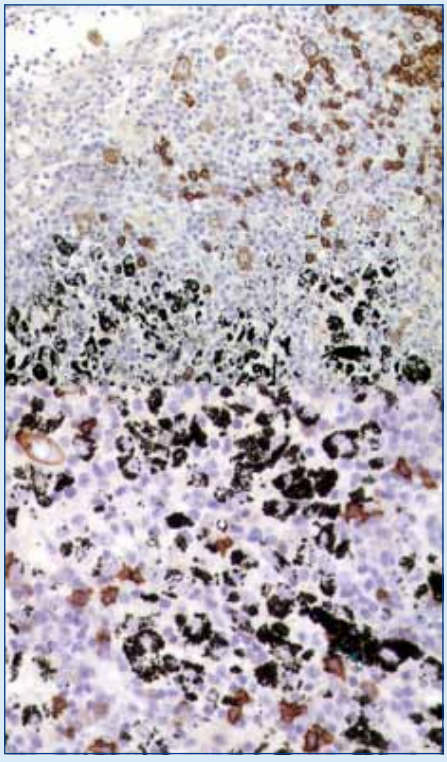

Table 1. Causes of lymphadenopathy

Localized or regional lymphadenopathy	Infections (involving skin, oral maxillary and genitourinary, e.g. lymphogranuloma venereum caused by *Chlamydia trachomatis*)
	'Cat scratch disease' infection with the bacterium *Bartonella henselae* causes painful enlarged regional lymphadenopathy associated with fever
	Primary haematological malignancy, e.g. Hodgkin's lymphoma, which typically spreads contiguously, i.e. 'from one lymph node to another'
	Other malignancies metastasizing to lymph nodes by local or distant spread
Generalized lymphadenopathy	Infections, e.g. viral (Epstein–Barr virus, cytomegalovirus, human immunodeficiency virus, rubella), bacterial (tuberculosis, syphilis) or protozoal (toxoplasmosis, leishmaniasis)
	Lymphoproliferative and myeloproliferative disorders
	Autoimmune (e.g. systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome)
	Dermatopathic (e.g. eczema, psoriasis)
	Drugs (e.g. allopurinol, carbamazepine, phenytoin, penicillins, atenolol, captopril, isoniazid)

From Brown and Skarin (2004)

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tion of B-lymphocytes, sparing the patient an unnecessary lymph node biopsy. As a general rule, any lymph node >1 cm, which persists for 6–8 weeks or longer, should be biopsied unless the cause is known.

Epstein–Barr virus infection (infectious mononucleosis) most commonly causes marked enlargement of the jugular digastric nodes in the neck, pharyngitis and tonsillar inflammation; this clinical picture is seen in cases of streptococcal pharyngitis. In children, rubella presents with fever, rash and lymphadenopathy which, although often widespread, characteristically affects the posterior occipital and cervical lymph nodes.

The most common site of lymph node spread with breast cancer is the axilla. Occasionally patients present with axillary lymphadenopathy without a clinically or radiologically detectable primary in the breast. Isolated supraclavicular fossa nodes are unusual as an initial presentation, but may be a site of isolated relapse in a patient with a previously treated breast cancer. Enlarged internal mammary nodes are occasionally seen on imaging without any clinically enlarged axillary nodes being evident.

Seminomas metastasize in a predictable manner, spreading to the retroperitoneal nodes before disseminating elsewhere. It is unusual to find metastatic seminoma without retroperitoneal involvement. This is the reason why adjuvant radiotherapy to the retroperitoneum was developed as standard therapy for stage I seminoma patients, whereas for non-seminomatous germ cell tumours metastases can occur in widely differing lymph node sites.

Clinical approach to assessing lymphadenopathy

History

- Distribution, size of lymph nodes (are they enlarging?)
- Duration – benign causes are usually self-limiting, >6 weeks duration is an indication to biopsy unless the cause is certain
- Painful lymphadenopathy (more common in reactive lymphadenopathy but may occur with malignancy)
- Alcohol-induced pain (this may be seen in Hodgkin's lymphoma and is so specific that it is possible to stage a patient depending on where a patient notices pain after consuming alcohol)
- Symptoms suggestive of local mass effect
- Constitutional symptoms, 'B' symptoms – fever, drenching night sweats, weight loss >10% over the preceding 6 months
- Risk factors for malignancy
- Foreign travel
- Risk factors for diseases that may present with lymphadenopathy, e.g. ask about skin disorders – dermatopathic lymphadenopathy is a common finding in patients with chronic skin conditions, and ask about risk factors for HIV
- New medications (*Table 1* lists drugs commonly associated with lymphadenopathy)
- If considering the need for a biopsy, enquire about any bleeding symptoms after haemostatic challenges, e.g. dental extractions or operations, and drugs such as heparin, aspirin and warfarin, which may interfere with blood coagulation.

Examination

General examination

- Does the patient appear cachectic, jaundiced or anaemic?
- Are there signs of superior vena caval obstruction such as facial swelling?
- Are there signs of petechiae or bruising?
- Examine for hepatosplenomegaly.

When examining lymph nodes

- Compare both sides
- Examine local structures draining to involved enlarged nodes, e.g. breast examination if axillary lymphadenopathy or leg and external genitalia if inguinal lymphadenopathy is present
- Check for size (>1 cm is pathological in all nodal groups except inguinal where >2 cm requires full investigation)
- Feel for consistency – malignant nodes often feel hard, infective nodes may be tender, in lymphoma the nodes are sometimes described as 'rubbery'. The consistency is not a reliable guide to the underlying pathology
- Check for mobility – non-mobile, fixed nodes may indicate malignancy and may cause overlying skin induration. It is common practice to examine lymph nodes in the head and neck from behind the patient
- Palpate for submental, submandibular, pre- and post-auricular, posterior occipital, cervical, supraclavicular nodes (left supraclavicular node, Virchow's node in gastric carcinoma).

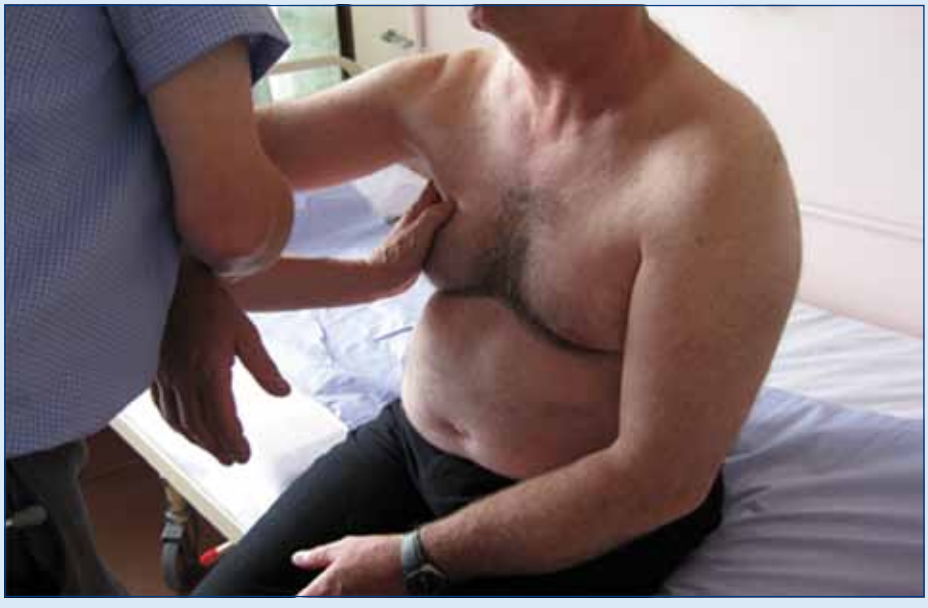
Examination of specific sites

Figure 2 gives a suggested approach for examination of the axillary lymph nodes. Examine the patient from the front or side and use your left hand to examine the right axilla and vice versa. Palpate the apex, medial, anterior and posterior walls.

Examine the epitrochlear node with the patient's elbow partially flexed.

Examine the horizontal and vertical chain of the inguinal nodes.

Figure 2. Examination for axillary lymphadenopathy.



The anatomical distribution of regional lymph nodes is illustrated in *Figure 3*.

Investigations

Further tests should be guided by the clinical presentation (*Table 2*).

Imaging

Ultrasound scanning is a useful first-line non-invasive approach to confirm the size and location of the lymph node swelling and potentially identify signs of pathological nodes as a target for biopsy.

Biopsies

The biopsy should be directed at the most 'abnormal' node. Although biopsies from the groin are easily accessible, they have the lowest diagnostic yield and it is preferable to biopsy a different site if possible (Habermann and Steensma, 2000). In malignant disorders, high uptake on fluorodeoxyglucose positron emission tomography scanning may help identify an involved node.

Options for biopsy include fine needle aspiration, core biopsy and excision node biopsy. Ultrasound or computed tomography-guided biopsies are often used. Fine needle aspiration is a quick and relatively straightforward procedure, which can be done under local anaesthetic. Fine needle aspiration may provide useful information such as confirmation that the swelling is a lymph node, provide samples for microbiology, and differentiate between neoplastic and non-neoplastic causes and secondary malignancies. However, the major disadvantage of a fine needle aspiration is that there is often insufficient cellular material obtained for an accurate morphological diagnosis. The addition of immunophenotyping, molecular and cytogenetic techniques has increased the diagnostic yield from fine needle aspiration samples. However, guidelines still recommend excision biopsy in cases where a lymphoproliferative disorder is suspected (Parker et al, 2010).

Further investigations if indicated are:

- Computed tomography or positron emission tomography-computed tomography: neck, chest, abdomen, pelvis for staging of cancer
- Bone marrow examination for staging of lymphoma.

Conclusions

A careful history and examination narrows the broad differential diagnosis of localized and generalized lymphadenopathy. Any lymph node >1 cm (or 2 cm for inguinal nodes) requires full assessment including fine needle aspiration followed by excision biopsy if necessary. BJHM

Figure 3. Diagram of regional lymph node groups.

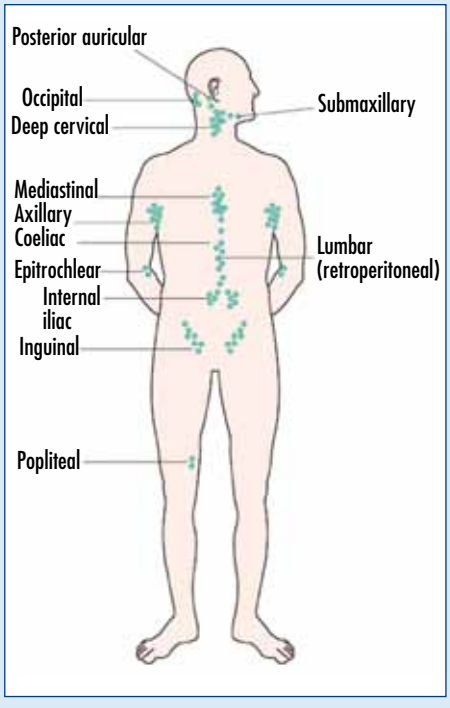


Figure 1 *is reproduced courtesy of Professor Kevin Gatter. NDCLS, Oxford. The authors would like to thank Dr Bernadette Lavery and Dr Andrew Protheroe for their helpful comments and contribution to this article, and to Dr Jonathan Pattinson for his assistance with the clinical demonstration.*

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Table 2. Helpful investigations

Investigation	Rationale
Full blood count, erythrocyte sedimentation rate	Infection, inflammation, bone marrow function
Blood film	Atypical lymphocytes suggestive of cytomegalovirus, Epstein–Barr virus or human immunodeficiency virus. Evidence of lympho- or myeloproliferative disorder on the blood film
Biochemistry: urea and electrolytes, liver function tests, C-reactive protein	Infection, inflammation, liver infiltration
Serology: cytomegalovirus, Epstein–Barr virus, human immunodeficiency virus, toxoplasmosis and syphilis	Infective cause
Autoimmune screen	Check for systemic lupus erythematosus or rheumatoid arthritis
Chest X-ray	Tuberculosis and other infections, primary or secondary malignancy, sarcoidosis

KEY POINTS

- Knowledge of local anatomy and structures draining into a lymph node group helps to determine causes of localized lymphadenopathy.
- Generalized lymphadenopathy often reflects systemic disease.
- Lymphadenopathy persisting for >6 weeks or associated with worrying features needs further assessment to exclude sinister causes.
- Ultrasound is a useful first-line non-invasive imaging modality.
- Histological confirmation of lymphoproliferative conditions is best attained with whole node excision biopsy.