# Lymphadenopathy in children: refer or reassure?

David King, Jagadeesh Ramachandra, Daniel Yeomanson

Department of Paediatric Oncology, Sheffield Children's Hospital NHS Foundation Trust, Sheffield, UK

**Correspondence to**
Dr Daniel Yeomanson, Department of Paediatric Oncology, Sheffield Children's Hospital NHS Foundation Trust, Western Bank, Sheffield S10 2TH, UK; Daniel.Yeomanson@sch.nhs.uk

Received 22 May 2013
Revised 19 November 2013
Accepted 2 December 2013
Published Online First 2 January 2014

**To cite:** King D, Ramachandra J, Yeomanson D. *Arch Dis Child Educ Pract Ed* 2014;**99**: 101–110.

## INTRODUCTION

Fareed, a 15-year-old British boy of Pakistani origin, was brought to his general practitioner (GP). His parents had become concerned about a 'lump' which had recently appeared on his neck and had now been present for approximately 2 weeks. Fareed had been unwell in the last fortnight with a history of a mild fever, coryzal symptoms and a sore throat. These symptoms had resolved although he was still feeling quite tired. There was no history of night sweats, weight loss or pruritus and he had not noticed any unusual lumps in other places.

There was no significant past medical history. Fareed was fully immunised. He was not taking regular medication and had no allergies. His parents were originally from Pakistan but he had never been abroad. There was no history of diseases in the family and no contacts with tuberculosis. There were also no pets.

On examination Fareed appeared well. His height (170 cm, just above 50th centile) and weight (63 kg, just below the 75th centile) were recorded. There was no pallor, jaundice or petechiae. His pharynx was a little inflamed and he had mildly enlarged tonsils without exudate. A 2.5-cm lymph node was palpable in the left posterior triangle of the neck. This was firm, mobile and mildly tender, but there was no inflammation or induration of the overlying skin. There were no other palpable nodes in the neck, supraclavicular fossa, axillae or groin and no hepatosplenomegaly.

After considering the clinical presentation and examination findings, a diagnosis of reactive lymphadenopathy was made. In the absence of any signs of significant bacterial infection, supportive care was recommended. A throat swab was sent to rule out Group A streptococcal infection. In view of the 2.5 cm lymph node, review was planned in 3 weeks.

## COMMENT

Lymphadenopathy refers to lymph nodes which are abnormal in size, number or consistency. The peak incidence in childhood is not known but it is certainly common with several studies demonstrating that 45% to 57% of otherwise healthy children may have palpable lymph nodes at any one time.[1 2] In the vast majority of cases lymphadenopathy represents a benign response to a self-limiting infection but occasionally it may indicate the presence of a more serious disorder, including malignancy. The management of these children therefore creates a great deal of consternation for parents, GPs and paediatricians alike.

A thorough history and examination is essential when assessing a child with lymphadenopathy. Box 1 highlights the important points to cover in the history. Because infections are the most common cause of acute or chronic lymphadenopathy, it is important to focus on the presence of, or recent exposure to infection.[3] It is also important to document the duration and site of the lymphadenopathy and whether there has been any change in the size of any lymph nodes over time. Recent exposure to animals, travel abroad, medication history and immunisation status may also give clues to the possible aetiology.

Box 2 summarises the main areas for examination in a child with lymphadenopathy.

Examination should start by measuring the child's temperature and plotting their height and weight. The enlarged group of lymph nodes should be palpated and an attempt should be made to describe their size, location, consistency, mobility and if they are tender. It is also important to examine other groups of lymph nodes to determine whether the lymphadenopathy is localised or generalised (see figure 1). The presence of localised lymphadenopathy, together with its

**Box 1 History of a child with lymphadenopathy**

- Age—some infections have a predilection for specific age groups
- Characteristics of the lymphadenopathy:
  - Site?
  - Duration?
  - Time course of growth?
  - Overlying skin changes, for example, discolouration, induration?
  - Painful or fluctuant?
  - Other nodes involved; generalised or local?
- Recent infections:
  - History of recent URTI?
  - Gum or tooth infection; mouth ulcers?
  - Respiratory symptoms: cough, shortness of breath, orthopnoea?
  - Skin infections: cellulitis or impetigo?
  - Sexually transmitted disease (if sexually active)?
- Constitutional symptoms:
  - Fatigue?
  - Weight loss: how much over what time period?
  - Night sweats?
  - Fever: constant or periodic?
  - Bleeding or easy bruising?
  - Joint pain or swelling; which joints affected?
  - Rash?
- History of foreign travel: countries visited?
- Exposure to cats, other pets or wild animals?
- Exposure to tuberculosis via family contacts or from endemic area?
- Recent immunisations?
- Medications?

**Box 2 Examination of a child with lymphadenopathy**

- General observation
  - Is the child well or ill?
  - Plot height and weight
- Examination of lymphadenopathy
  - Size
  - Location
  - Fixation
  - Consistency
  - Tenderness
  - Overlying skin changes, for example, discolouration, induration
  - Examination of other lymph nodes, for example, axillae/inguinal regions
- Head and neck
  - Scalp infection, for example, impetigo
  - Conjunctivitis, specify if purulent or non-purulent
  - Ear, nose and throat—signs of infection, mouth ulcers, dental disease
- Skin
  - Rashes
  - Localised infection for example, cellulitis/impetigo
  - Petechiae/eccyhmoses/purpura
- General examination
  - Cardiovascular
  - Respiratory
  - Abdominal—particularly for hepatosplenomegaly

anatomical location, often helps to narrow the differential diagnosis. Table 1 details important causes for localised cervical lymphadenopathy according to the anatomical location.

Careful assessment of the size of the enlarged nodes is important as bigger nodes are associated with a higher likelihood of more serious pathology, and accurate measurement allows for meaningful comparison over time. In a study of 123 children and young adults undergoing a biopsy for peripheral lymphadenopathy, lymph nodes greater than 2 cm in diameter increased the chance of a diagnosis of either significant infection, sarcoidosis or malignancy.[4] Conversely, a palpable lymph node measuring less than 1 cm is probably normal.[5] The site of the enlarged nodes is also significant. Lymph nodes palpated in the supraclavicular region often reflect mediastinal disease and should prompt the request of a chest X-ray (CXR). In a study of 75 children undergoing a biopsy for lymphadenopathy, all patients with supraclavicular lymphadenopathy were found to have significant pathology.[6]

Other areas to examine include the skin for the presence or absence of impetigo, eczema, rashes or petechiae. Localised skin infections or eczema can cause reactive lymphadenopathy while petechiae may indicate thrombocytopenia due to bone marrow involvement by a malignant process. An eye and thorough ENT examination should be also undertaken to look for evidence of infection or inflammation. It is also important to examine the abdomen to exclude hepatosplenomegaly.

A diagnosis of Kawasaki's disease should be considered in any child with acute cervical lymphadenopathy, especially if they also have a fever. Classically Kawasaki's disease is diagnosed when a child has had a fever for 5 days or longer together with four symptoms out of the following five: erythema and desquamation of the hands, a bilateral non-purulent conjunctivitis, a maculopapular rash, inflammation of the mouth, lips and tongue and cervical lymphadenopathy greater than 1 cm. However, on occasions Kawasaki's disease can initially present with only fever and cervical lymphadenopathy.[7] Clinicians should therefore not dismiss the possibility of Kawasaki's disease, even if the child does not meet the diagnostic criteria when they are first examined.

## CLINICAL REASONING

In the case described, the actions of the GP are entirely appropriate. Fareed is systemically well and

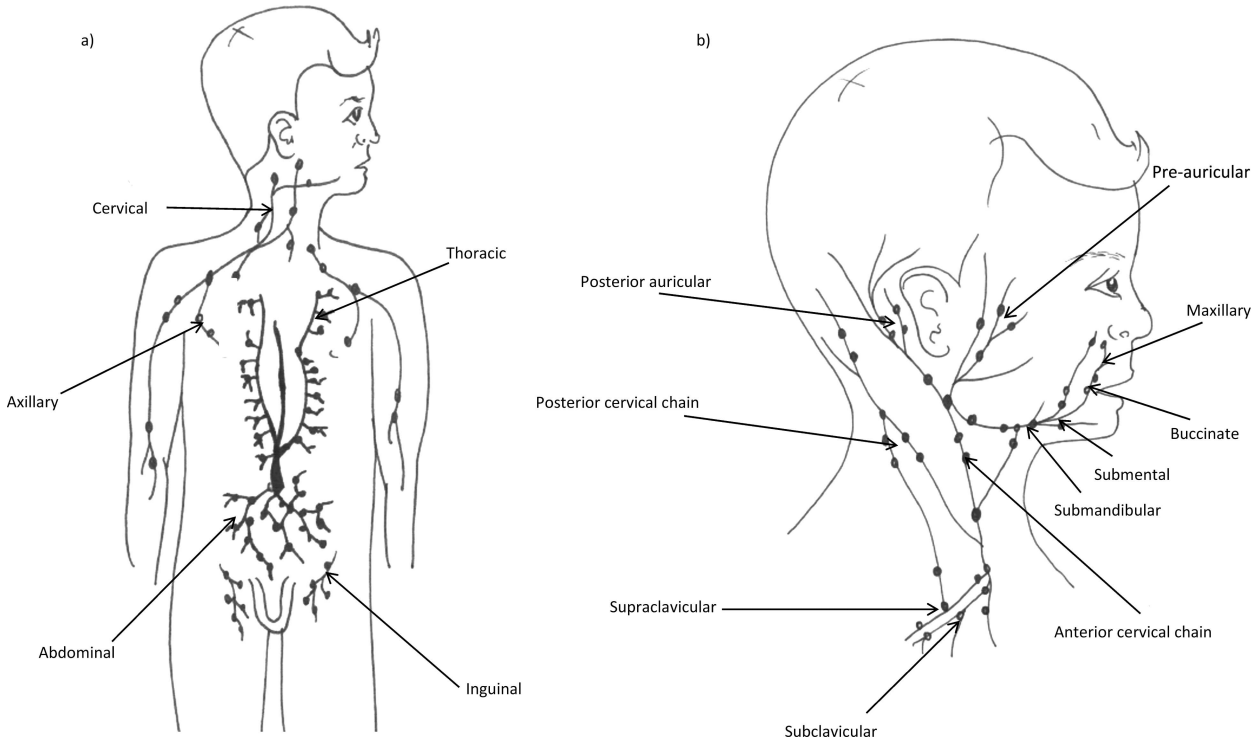


**Figure 1** (A) Nodal regions in the body (B) Lymphatic drainage and nodal regions in the head and neck.

only has one palpable cervical lymph node. The fact the node has only recently enlarged, the otherwise normal examination and the recent upper respiratory tract infection support a diagnosis of reactive lymphadenopathy. Some authors advocate an empirical course of a broad spectrum antibiotic such as co-amoxiclav in this situation, based on the rationale that staphylococcal or streptococcal infection can often trigger cervical lymph node enlargement.[3] The risks associated with antibiotic use including possible adverse effects and the development of antibiotic resistance should be considered by the clinician and, if there is no clear evidence of localised infection, a period of observation is probably equally valid. In this case the GP has taken a throat swab but has not started antibiotics, which is sensible. What is most important is that Fareed returns for review of his lymphadenopathy in 3–4 weeks or sooner if he develops any new symptoms.

## REVIEW BY GP AFTER 3 WEEKS

Three weeks later Fareed returned to the GP for review. He still reported feeling very tired at the end of the day but was otherwise well. The enlarged cervical lymph node was present but had not changed in size or nature. There were no new systemic symptoms and the patient's weight was stable. Full clinical examination identified no other lymphadenopathy or hepatosplenomegaly.

**Table 1** Cervical lymph node drainage and selected causes of localised lymphadenopathy (partly adapted from Ferrer[28])

| Anatomical location | Lymphatic drainage | Selected causes of localised lymphadenopathy |
|---|---|---|
| Anterior cervical | Throat, posterior pharynx, tonsils, thyroid gland | Local infections in the ear, nose and throat, infectious mononucleosis, cytomegalovirus infection, toxoplasmosis |
| Posterior cervical | Scalp and neck, thorax, cervical and axillary nodes | Local infections in the scalp, tuberculosis, lymphoma, head and neck malignancy |
| Tonsillar | Tonsillar and posterior pharyngeal regions | Infections of the throat |
| Submandibular | Floor of the mouth, submandibular gland, tongue, lips, conjunctivae | Dental disease, infections in the ear, nose, throat and eyes |
| Submental | Lower lip, floor of mouth, tip of tongue, cheek | Dental disease, local infections |
| Supraclavicular | Mediastinum, lungs oesophagus. abdomen via thoracic duct | Lymphoma, thoracic or gastrointestinal cancer |

## COMMENT

The management of lymphadenopathy in children is often dictated by whether the presentation is acute (less than 2 weeks duration), subacute (2–6 weeks duration) or chronic (over 6 weeks duration). This classification is somewhat arbitrary and many disease processes are associated with symptom duration that fits into more than one category. In general, acute lymphadenopathy is commonly caused by a bacterial or viral infection while chronic lymphadenopathy is more likely to be due to an opportunistic infection or malignant process. Subacute lymphadenopathy encompasses children who do not meet the definition for acute or chronic lymphadenopathy and has a wide range of aetiologies.

Investigations are rarely indicated for acute lymphadenopathy. In contrast, they are more important in establishing the diagnosis in subacute or chronic lymphadenopathy. In the case described, the patient has had an enlarged cervical lymph node for around 6 weeks. He can therefore be considered to have chronic lymphadenopathy making further evaluation prudent. Table 2 details possible causes for chronic lymphadenopathy and their associated clinical features.

## INVESTIGATIONS BY THE GP

After reviewing Fareed, the GP requested a full blood count (FBC) and film, erythrocyte sedimentation rate (ESR), liver function tests (LFTs) and C-reactive protein (CRP) and testing for glandular fever (infectious mononucleosis). The throat swab which had been performed at the first consultation was negative.

## COMMENT

The wide list of differential diagnoses for a child with chronic lymphadenopathy means that an attempt must

**Table 2** Conditions associated with chronic lymphadenopathy and their associated clinical features

| Diagnosis | Clinical features in addition to lymphadenopathy |
|---|---|
| Infections | |
| EBV | Fever, pharyngitis, maculopapular rash, fatigue, myalgia, mild hepatosplenomegaly, hepatitis |
| CMV | Often asymptomatic; occasionally fever, splenomegaly, fatigue, hepatitis |
| Primary HIV infection | Fever, rash, headache, pharyngitis, myalgia, mouth ulcers |
| Herpes simplex | Mouth ulcers, fever, fatigue |
| Toxoplasmosis | Often asymptomatic; occasionally fever, malaise, night sweats, myalgia |
| Borrelia burgdorferi | In endemic region, erythema migrans, fever, arthritis, CNS symptoms, myocarditis, AV block, dilated cardiomyopathy |
| Granulomatous diseases | |
| Bartonella henselae (cat-scratch disease) | Erythematous lesion at site of scratch from cat, fever, headache, malaise |
| Atypical mycobacterium | Often isolated lymphadenopathy, with discolouration of overlying skin, occasionally disseminated infection |
| Mycobacterium tuberculosis | Fever, weight loss, respiratory symptoms, night sweats, patient from endemic area or with risk factors |
| Sarcoidosis | Fever, night sweats, weight loss, can have respiratory, neurological, skin and cardiovascular symptoms |
| Neoplastic | |
| Lymphoma | Fever, weight loss, fatigue, night sweats, pruritus |
| Leukaemia | Fatigue, pallor, bleeding/bruising, weight loss |
| Metastases from another primary | Variable according to primary malignancy |
| Endocrine | |
| Hyperthyroidism | Weight loss, tremor, anxiety, sweating, diarrhoea, intolerance of heat, goitre, exophthalmos |
| Miscellaneous | |
| Kawasaki's disease | Fever, non-purulent conjunctivitis, erythema, swelling and desquamation of hands and feet, rash, oral mucosal changes, irritability |
| Medications | Variable according to medications |
| Postvaccination | Prior history of vaccination |
| Lipid storage disorders | Developmental delay/regression, organomegaly, bone marrow dysfunction, skeletal abnormalities, failure to thrive |
| Juvenile idiopathic arthritis | Polyarthritis, fever, rash, weight loss |
| Systemic lupus erythematosus | Fatigue, weight loss, fever, rash, multisystem involvement including musculoskeletal, neurological, pulmonary, cardiac, haematological manifestations |

CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein-Barr virus.

be made to rationalise investigations according to the history and examination. Investigations which are helpful in a case such as this are detailed below. A suggested approach to management is detailed in figure 2.

### Blood tests

Sensible baseline blood tests for a child with chronic lymphadenopathy include a FBC and film and inflammatory markers such as ESR and CRP. It is important to note that a normal FBC and film does not exclude the presence of lymphoma but it does make leukaemia unlikely.[8] If there is a suspicion of a viral infection, LFTs may be abnormal and should be checked. Lactate dehydrogenase is a marker of cell turnover and is raised in lymphoma but it is far from specific for this diagnosis and is rarely useful in the investigation of a child with lymphadenopathy.[9] It certainly cannot be used as a screening test for lymphoma.

### Serological investigations

Depending on the clinical history, specific serological investigations may be indicated. Infectious mononucleosis, secondary to Epstein–Barr virus (EBV), is a common cause of lymphadenopathy. Children infected with EBV have a wide spectrum of illness. Many are asymptomatic but a small number may be critically ill at presentation. Signs and symptoms include fever, pharyngitis and lymphadenopathy, characteristically with symmetrical involvement, predominantly of the posterior cervical chain. Axillary and inguinal lymph nodes may also be involved. Nodes can be large and typically peak in size over the first week of the illness, gradually subsiding over the next few weeks. Other features of the illness include fatigue, malaise, splenomegaly, atypical lymphocytosis and rash appearing after exposure to amoxicillin.[10]

Various diagnostic tests for EBV infection exist. These include the heterophile antibody agglutination (monospot) test, although this can produce false negatives within the first 3 weeks of the illness, especially in children younger than 4 years old.[11] More sensitive tests have been developed which are useful if the monospot test is negative and clinical concerns persist. EBV viral capsid antigen (VCA) IgM and EBV early antigen antibodies are usually detectable immediately and disappear with 4–8 weeks of the onset of symptoms. IgM antibodies are not detected in association with chronic infection and their presence can therefore be used to confirm primary infection. VCA IgG and EBV nuclear antigen antibodies appear much later in the course of the illness and during convalescence.[10] If serological results are equivocal or negative despite a convincing clinical picture, they should be rechecked in 2–4 weeks.

Additional serological tests may also be indicated for selected children with lymphadenopathy. *Borrelia burgdorferi*, transmitted by tick bites, causes Lyme disease which can often present with lymphadenopathy. Infected ticks are endemic in large parts of the UK and testing should be considered if patients have been in affected areas, or if there is a history of

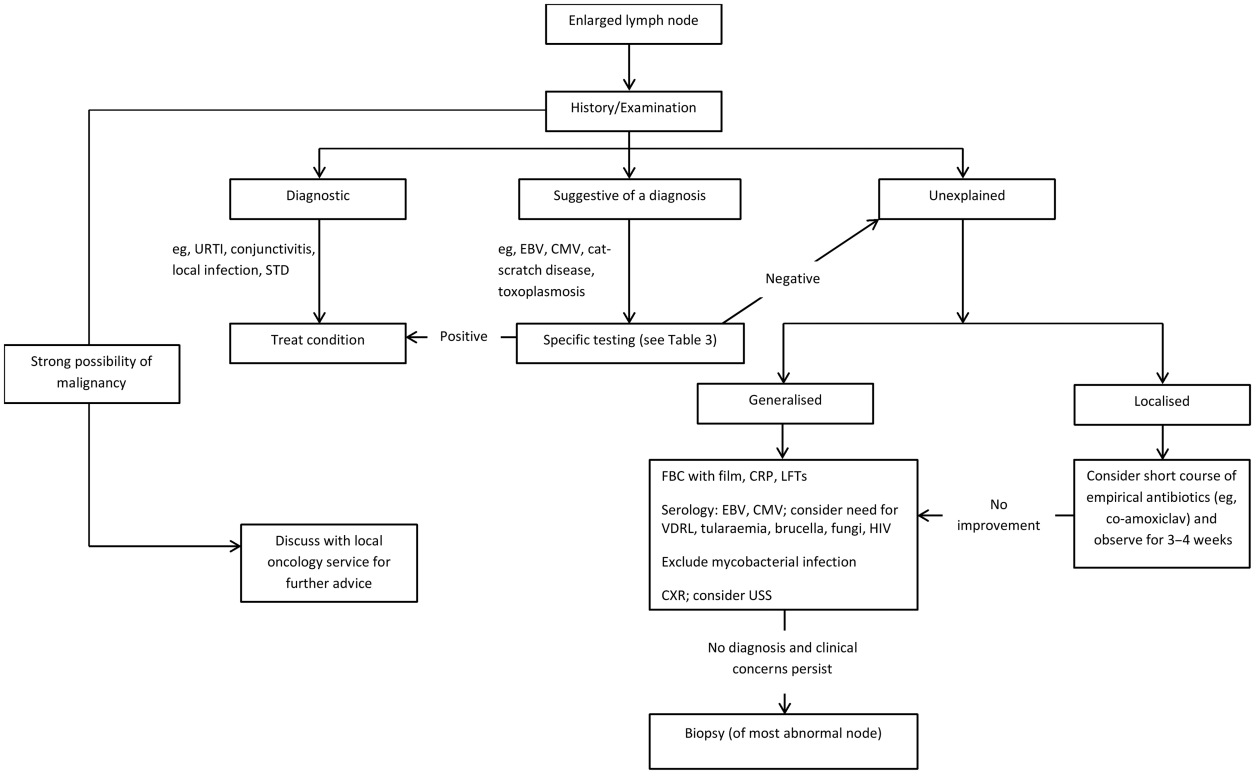


**Figure 2** Management of a child with lymphadenopathy adapted from Nield and Kamat[3] and Friedmann[11].

migratory skin rash (erythema migrans). Less common infectious causes may need to be looked for based on the clinical history. Potential organisms include *bartonella henselae* (the causative organism of cat-scratch disease), toxoplasmosis and cytomegalovirus (CMV). Rarely brucellosis, syphilis, tularaemia, histoplasmosis and coccidiomycosis can be associated with lymphadenopathy and should be tested for if clinical symptoms support one of these diagnoses. Primary HIV infection is often associated with cervical or generalised lymphadenopathy and is easy to overlook as a potential cause.[12] Patients and their families should be asked about possible risk factors and, if there is any chance of infection, serological testing should be arranged after appropriate counselling.

#### Testing for mycobacterial infection

The possibility of mycobacterial infection must always be considered in any patient with chronic lymphadenopathy. This is particularly pertinent in this case, given Fareed's ethnic background. Screening for mycobacterial infection can be performed using either the Mantoux tuberculin (skin) test or interferon-γ (blood) test.[13] A strongly positive intradermal tuberculin test (>15 mm) suggests infection with *Mycobacterium tuberculosis*, whereas a lesser reaction to tuberculin skin testing is more consistent with non-tuberculous mycobacterial infection or previous Bacillus Calmette–Guérin (BCG) vaccination.

#### Chest X-ray

Plain X-rays are seldom necessary in acute lymphadenopathy but are much more valuable when evaluating a child with subacute or chronic lymphadenopathy. CXR may suggest involvement of the mediastinal lymph nodes or other pulmonary disease such as tuberculosis. CXR is essential if the child has any respiratory symptoms such as orthopnoea or stridor, regardless of how long the lymphadenopathy has been present. Patients found to have mediastinal widening on CXR should be discussed with the paediatric oncology team and a decision made about whether immediate transfer is necessary.

## CLINICAL REASONING

In this case, Fareed appears well but can be considered to have chronic lymphadenopathy as he has had an enlarged cervical lymph node for around 6 weeks. Further investigations are therefore appropriate. The GP has requested a FBC and film, ESR, LFTs and CRP which, as detailed above, are useful investigations for a child with chronic lymphadenopathy. A glandular fever screen is helpful, because if it was positive, Fareed could continue to be observed in primary care. A CXR should also be considered to exclude hilar lymphadenopathy which could indicate tuberculosis, a lymphoma or more rarely sarcoidosis. If the diagnosis remains unclear after these investigations, Fareed should be referred to secondary care for further evaluation.

## REVIEW BY GP AFTER 6 WEEKS

Fareed was reviewed by his GP 2 weeks later. The cervical lymph node was similar in size but perhaps a little larger. He was otherwise well with no new symptoms although he continued to complain of lethargy. The FBC and film, ESR, LFTs and CRP were all within normal limits. A monospot test and EBV VCA IgG and IgM were also negative. Fareed was referred to a general paediatrician and an ultrasound scan of the lymph node was requested.

## COMMENT

An ultrasound may be requested in children with lymphadenopathy, especially if there is just one enlarged node or group of nodes. In acute lymphadenopathy it is primarily of value in assessing whether a swelling is nodal in origin or is due to another soft tissue mass. In addition it may detect an abscess suitable for drainage.

In patients with subacute or chronic lymphadenopathy, ultrasound may be used in an attempt to determine whether the nodal enlargement is neoplastic or infectious in origin. There are a number of distinguishing features that help to separate abnormal from normal lymph nodes on ultrasound. It has been shown that malignant nodes are more likely to have a short axis:long axis ratio greater than 0.5 compared to benign nodes.[14] Absence of an echogenic hilus may indicate the presence of an infiltrating tumour or alternatively tuberculosis and is a concerning sign.[14] Assessment of the vascularity of the lymph node with colour Doppler ultrasound is also valuable. Inflammatory lymph nodes are typically more vascularised but without changes in the hilar vessel architecture. Conversely, malignant lymph nodes present peripheral or mixed vascularity and loss of the hilar type of vascularisation.[15]

However, although ultrasound may be useful in the assessment of a child with lymphadenopathy, it cannot be used to definitively exclude malignancy. For this reason, some clinicians may recommend an excision biopsy of a persistent large lymph node without undertaking an ultrasound or even if a previous ultrasound appears reassuring.

## REVIEW BY GENERAL PAEDIATRICIANS

Fareed was reviewed 2 weeks later by a general paediatrician. The history was revisited. He was normally fit and well with no recurrent infections. He had never been sexually active and there were no other risk factors for HIV infection. He had not been in contact with any animals and he had not travelled abroad. There was a history of elderly relatives visiting from Pakistan around 6 weeks before the cervical lymph node appeared.

On examination he now had a large cervical lymph node measuring around 3 cm. There were no other significant findings on examination.

A CXR was arranged which showed hilar lymphadenopathy but clear lung fields. A Mantoux test was performed and was negative. Ultrasound of the neck showed a cluster of nodes with abnormal echotexture in the left neck, with the largest measuring 3 cm in the long axis. Following review of results Fareed was referred to the surgeons for a lymph node biopsy.

## CLINICAL REASONING

A negative Mantoux test in an immunocompetent child makes the diagnosis of tuberculosis unlikely. Hilar lymphadenopathy on the CXR in association with chronic lymphadenopathy has a number of differential diagnoses but it is clearly important to exclude a malignant process, especially in view of the ultrasound findings. Fareed therefore requires a biopsy of the enlarged cervical lymph node.

## COMMENT

The decision of whether or not to perform a lymph node biopsy in a child with lymphadenopathy can sometimes be a difficult one. In the majority of cases the biopsy simply shows reactive hyperplasia[16] but it is often considered the only definitive way to exclude malignancy or mycobacterial infection.

Box 3 lists possible indications for lymph node biopsy. Any of these features alone may prompt the clinician to undertake a lymph node biopsy but the presence or absence of specific features should also be considered when applying these criteria. If the child appears unwell with fever, weight loss and night sweats and the diagnosis is unclear they should be referred for a biopsy sooner rather than later. Conversely, if only one feature is present, the child is well and a confident clinical diagnosis can be made, biopsy is not necessarily indicated.

**Box 3 Features which may prompt a lymph node biopsy in a child with peripheral lymphadenopathy adapted from Nield and Kamat[3]**

- Lymph node size >2 cm
- Node increasing in size over 2 weeks
- No decrease in node size after 4–6 weeks
- Node not returned to baseline after 8–12 weeks
- Abnormal chest X-ray
- Presence of a supraclavicular node
- Presence of systemic signs and symptoms
  - Fever
  - Weight loss
  - Night sweats
  - Hepatosplenomegaly

The diagnostic yield of biopsies in children with lymphadenopathy is affected by the site of the lymph node, the experience of surgeons and histopathologists and the pathological techniques available. If possible, the largest and most abnormal node should be biopsied. In general, inguinal and axillary lymph nodes are less likely to be diagnostic while the highest yield is obtained with a supraclavicular or lower cervical chain node.[11] Even after a biopsy as many as 40% to 50% of patients may not receive an exact aetiology for their lymphadenopathy although this does depend on the geographical location and local burden of disease.[6 17] Occasionally children may need a second biopsy or bone marrow examination if clinical concerns persist.

There has been increasing discussion in recent years about the possible role of fine-needle aspiration (FNA) in children with persistent lymphadenopathy. FNA is capable of differentiating between benign and malignant peripheral lymphadenopathy in children and can reduce the number requiring an open biopsy.[18] However, many clinicians worry about false negatives and the possibility of forming a sinus tract as a complication in mycobacterial infection. If malignant disease is identified, there may also be insufficient tissue to allow proper classification, necessitating a further biopsy. Additionally, many children find FNA a frightening procedure without a general anaesthetic and, if a general anaesthetic is to be performed, it is probably more sensible to perform an excision biopsy. At present FNA is therefore mainly restricted to resource-poor settings where surgical and histopathological services are limited.[19]

It is worth emphasising the need to obtain a CXR before administering a general anaesthetic to a child who requires a biopsy for lymphadenopathy. The risk of children suffering an unexpected cardiorespiratory collapse during anaesthetic induction due to a mediastinal mass is well described.[20] This is usually secondary to extrinsic compression of the airway, obstruction to venous return or obstruction to the output of the heart. If a child is discovered to have a mediastinal mass on CXR they should be discussed with a paediatric oncologist before any further investigations are undertaken.

## RESULTS OF THE BIOPSY AND FURTHER PROGRESS

Fareed had an open biopsy of a 3-cm cervical lymph node from the left posterior triangle of the neck without any complications. Subsequent histopathological examination demonstrated abnormal lymph node architecture consisting of an infiltrate composed of numerous Reed-Sternberg and Hodgkin cells with a background of lymphocytes and eosinophils. Immunohistochemical staining showed these neoplastic cells were positive for CD30, CD15 and MUM-1. They were negative for Bcl-6 and CD20. The

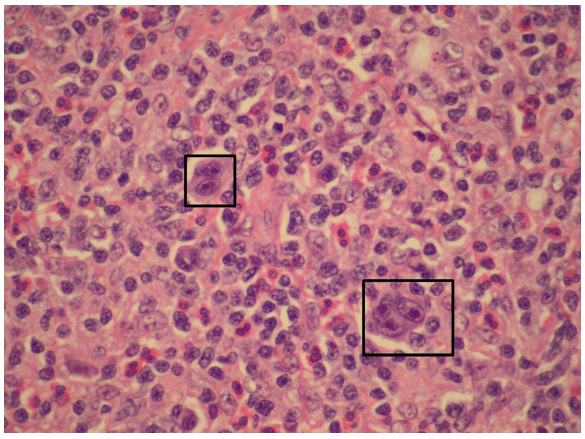

**Figure 3** Hodgkin's lymphoma histology showing classical Reed-Sternberg cells (see boxes) with a mixed cellularity background. H&E stain (×60).

diagnosis was therefore a nodular sclerosis subtype of classical Hodgkin lymphoma (HL).

## COMMENT

Approximately 1700 new cases of HL are diagnosed in the UK every year. There is an increased incidence in adolescence and early adulthood and again in patients aged 55 years and older.[21] It is currently the most common malignancy in adolescents aged 15–19.[22] HL is characterised histologically by large, clonal, multinucleated cells called Reed-Sternberg cells with a background environment consisting of an inflammatory infiltrate comprised predominantly of lymphocytes (see figure 3). Nodular sclerosis is the most common subtype of classical HL and tends to affect adolescents and young adults.[23]

Most children and adolescents with HL present with painless swelling of cervical, supraclavicular or axillary lymph nodes. Rarely inguinal lymphadenopathy may be the initial manifestation of HL. Systemic symptoms, also known as 'B' symptoms, consist of fever, weight loss or drenching night sweats and occur in up to one-third of patients. 'B' symptoms have prognostic significance and are less frequently observed in patients with limited-stage disease.[23]

**Box 4 Cotswold's revision of Ann Arbor staging system for Hodgkin's lymphoma (adapted from Townsend and Linch[29] and EURONET-PHL1—EudraCT-No: 2006-000995-33)**

Stage

1. Involvement of a single independent lymph node region or lymph node structure
2. Involvement of 2 or more lymph node regions on the same side of the diaphragm
3. Involvement of lymph node regions or lymph node structures on both sides of the diaphragm
4. Involvement of extranodal sites beyond 'E'-sites, for example, bone marrow, lung.

Annotations to Stage Definitions

A. No B symptoms
B. At least one of the following systemic symptoms
   a. Inexplicable weight loss of more than 10% within the last 6 months
   b. Unexplained persisting or recurrent temperature above 38°C
   c. Drenching night sweats
C. Involvement of a single extranodal site contiguous or proximal to known nodal site.

Staging in HL is based on modifications of the Ann Arbor system (see box 4). Contrast-enhanced CT of the neck, chest, abdomen and pelvis has historically been performed for staging. MRI is increasingly preferred due to excellent soft tissue resolution and absence of ionising radiation (see figure 4) although chest CT is still required to rule out lung infiltration. Ultrasound scanning is better than CT at detecting splenic lesions and should also be carried out. Functional imaging with 18F-fluorodeoxyglucose (18F-FDG) positron emission technology (PET) is used to stage disease and to provide a baseline for subsequent response assessment.

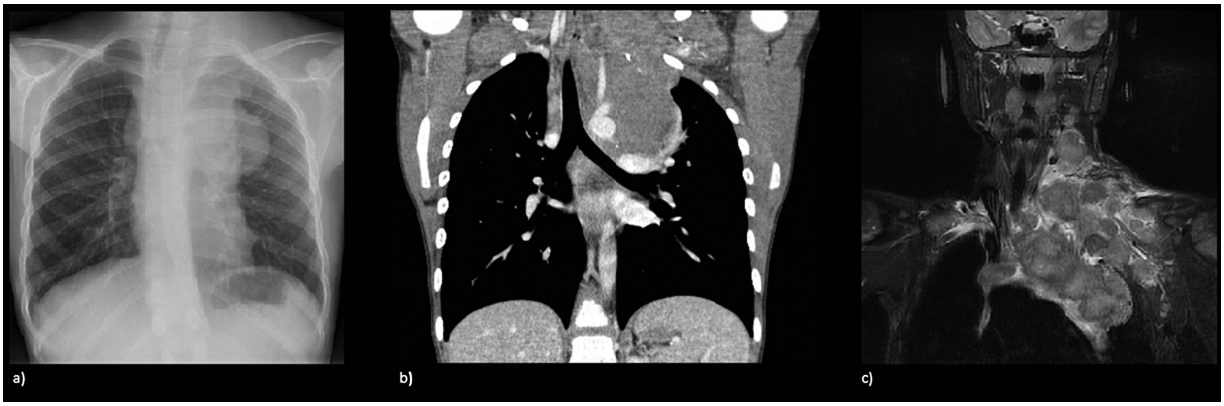


**Figure 4** Imaging of a mediastinal mass in a child with Hodgkin's lymphoma. (A) Plain chest radiograph demonstrating a mediastinal mass. (B) Reconstructed coronal CT chest with contrast. (C) Coronal STIR (short TI inversion recovery) MRI chest.

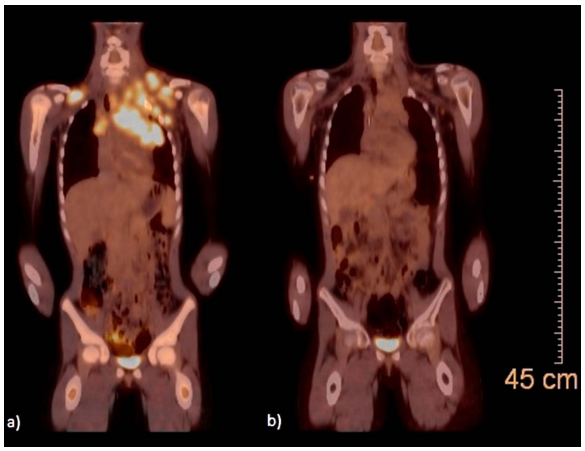


**Figure 5** Functional imaging with 18F-fluorodeoxyglucose (18F-FDG) PET in a child with Hodgkin's lymphoma. (A) 18F-FDG PET pretreatment. (B) 18F-FDG PET after two cycles of OEPA chemotherapy (vincristine, etoposide, prednisolone, doxorubicin).

Current HL therapy in children is stratified according to disease stage and response to initial induction chemotherapy. All patients receive two courses of chemotherapy followed by reassessment with cross-sectional imaging and FDG-PET (see figure 5). Patients with more extensive disease go on to receive two to four further courses of chemotherapy. Following completion of chemotherapy, patients whose response to the initial two courses of chemotherapy was inadequate receive involved field radiotherapy. Chemotherapy is generally given as an outpatient, and acute toxicity is relatively minor, although nausea and vomiting, alopecia and cytopenia are expected. Long-term effects of treatment for HL include osteoporosis, osteonecrosis, infertility, hypothyroidism (if thyroid within radiotherapy field), cardiomyopathy and secondary malignancy.[24] With stratified treatment the prognosis for childhood HL is excellent. In all children with Hodgkin's lymphoma the 5-year event free survival is around 95%[25] although in children with more advanced disease it is typically in the region of 70% to 80%.[26]

## Key points

- Lymphadenopathy in children is common and in the vast majority of cases is self-limiting.
- Occasionally it may represent a serious disease.
- A thorough history and examination, careful observation and appropriate investigations should help to decide which children require a biopsy or further treatment.
- In well children with localised, non-supraclavicular lymphadenopathy and no concerning systemic features a period of observation is usually the most appropriate management.

A minority of children with HL will be refractory to, or relapse, after initial treatment. The strategy for management of relapsed or refractory disease involves salvage chemotherapy, followed by high-dose chemotherapy and then autologous or allogeneic stem-cell transplantation in responding patients. Long-term survival in this group of patients is around 40% to 60%.[27]

## PROGRESS

Staging investigations revealed that Fareed was suffering from stage IA disease with only one group of lymph nodes affected. He was treated with two courses of chemotherapy (vincristine 1.5 mg/m$^2$ IV

## Multiple choice questions

1. Which one of the following tests should be performed in a child with chronic lymphadenopathy?
   A. Urea and electrolytes
   B. Lactate dehydrogenase
   C. Blood culture
   D. FBC and film
   E. Coagulation screen
2. What is the most common histological finding in children undergoing a biopsy for persistent lymphadenopathy?
   A. Mycobacterial infection
   B. Normal histology
   C. Benign reactive hyperplasia
   D. Lymphoma
   E. Cat-scratch disease
3. Which one of the following investigations should be performed before anaesthetising a child with lymphadenopathy?
   A. USS of lymph node
   B. Chest X-ray
   C. CT thorax
   D. Lung function tests
   E. PET scan
4. Which of the following signs or symptoms would **not** prompt a clinician to consider referral for a lymph node biopsy in a child with lymphadenopathy?
   A. Weight loss
   B. Night sweats
   C. Hepatosplenomegaly
   D. Lymph node measuring 1.5 cm
   E. Lymph node increasing in size over 2 weeks
5. Which of the following is **not** a long-term side effect of treatment for Hodgkin's lymphoma?
   A. Infertility
   B. Alopecia
   C. Hypothyroidism
   D. Osteoporosis
   E. Secondary malignancy

*Answers to the questions are on page 110.*

D1, 8, 15, etoposide 125 mg/m$^2$ IV D 1–5, prednisolone 60 mg/m$^2$ PO D1–15, doxorubicin 40 mg/m$^2$ IV D1, 15). Restaging with CT and MRI after two courses showed no evidence of residual disease. PET scan was negative. Fareed did not require radiotherapy and at follow-up 2 years later remains well with no treatment-related morbidity. He requires ongoing follow-up, which will include clinical examination, CXR, serial echocardiography and the offer of fertility assessment.

## COMMENT

Fareed had a favourable outcome. Importantly the GP ensured that he was followed up after the initial consultation rather than simply being reassured and discharged. Although the time from his initial presentation to the final diagnosis was around 2 months, the management of all clinicians involved in his care was appropriate, and the delay did not affect his prognosis.

**Acknowledgements** We are grateful to Kelly-Marie Nelson for providing the illustrations for figure 1 and Dr Paul French, consultant histopathologist in Sheffield Children's Hospital, for providing figure 3. The clinical history and images were amalgamated from a number of patients and were chosen to illustrate key points in the management of lymphadenopathy. We would like to thank those who provided permission for their clinical imaging to be used. DK would like to express his gratitude to the Yorkshire and Humber Postgraduate Deanery for funding his year as a Clinical Leadership Fellow in Research, during which this article was written.

**Contributors** DY conceived the idea for this review. All authors were involved in writing and reviewing the final manuscript.

**Competing interests** None.

**Provenance and peer review** Not commissioned; externally peer reviewed.

## REFERENCES

1 Larsson LO, Bentzon MW, Berg Kelly K, *et al*. Palpable lymph nodes of the neck in Swedish schoolchildren. *Acta Paediatr* 1994;83:1091–4.
2 Herzog LW. Prevalence of lymphadenopathy of the head and neck in infants and children. *Clin Pediatr* 1983;22:485–7.
3 Nield LS, Kamat D. Lymphadenopathy in children: when and how to evaluate. *Clin Pediatr* 2004;43:25–33.
4 Slap GB, Brooks JS, Schwartz JS. When to perform biopsies of enlarged peripheral lymph nodes in young patients. *JAMA* 1984;252:1321–6.
5 Gosche JR, Vick L. Acute, subacute, and chronic cervical lymphadenitis in children. *Semin Pediatr Surg* 2006;15:99–106.
6 Lake AM, Oski FA. Peripheral lymphadenopathy in childhood. Ten-year experience with excisional biopsy. *Am J Dis Child* 1978;132:357–9.
7 April MM, Burns JC, Newburger JW, *et al*. Kawasaki disease and cervical adenopathy. *Arch Otolaryngol Head Neck Surg* 1989;115:512–14.
8 Mitchell C, Hall G, Clarke RT. Acute leukaemia in children: diagnosis and management. *BMJ* 2009;338:b2285.
9 Ross AD, Abrahamson E. A review of the use of serum lactate dehydrogenase measurement in patients presenting to the paediatric emergency department. *Arch Dis Child* 2011;96(Suppl 1):A87.
10 Luzuriaga K, Sullivan JL. Infectious Mononucleosis. *N Engl J Med* 2010;362:1993–2000.
11 Friedmann AM. Evaluation and management of lymphadenopathy in children. *Pediatr Rev* 2008;29:53–60.
12 Das G, Baglioni P, Okosieme O. Primary HIV infection. *BMJ* 2010;341:c4583.
13 National Institute for Health and Clinical Excellence. *Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control (clinical guideline 117)*. 2011.
14 Chan JM, Shin LK, Jeffrey RB. Ultrasonography of abnormal neck lymph nodes. *Ultrasound Q* 2007;23:47–54.
15 Ahuja AT, Ying M. Sonographic evaluation of cervical lymph nodes. *AJR Am J Roentgenol* 2005;184:1691–9.
16 Knight PJ, Mulne AF, Vassy LE. When is lymph node biopsy indicated in children with enlarged peripheral nodes? *Pediatrics* 1982;69:391–6.
17 Hanif G, Ali SI, Shahid A, *et al*. Role of biopsy in pediatric lymphadenopathy. *Saudi Med J* 2009;30:798–802.
18 van de Schoot L, Aronson DC, Behrendt H, *et al*. The role of fine-needle aspiration cytology in children with persistent or suspicious lymphadenopathy. *J Pediatr Surg* 2001;36:7–11.
19 Khan RA, Wahab S, Chana RS, *et al*. Children with significant cervical lymphadenopathy: clinicopathological analysis and role of fine-needle aspiration in Indian setup. *J Pediatr* 2008;84:449–54.
20 Hack HA, Wright NB, Wynn RF. The anaesthetic management of children with anterior mediastinal masses. *Anaesthesia* 2008;63:837–46.
21 Ries LA, Eisner MP, Kosary CL, *et al*. SEER cancer statistics review, 1975–2002. Secondary SEER cancer statistics review, 1975–2002. http://seer.cancer.gov/csr/1975_2002/ (accessed March 2013)
22 Birch JM, Alston RD, Kelsey AM, *et al*. Classification and incidence of cancers in adolescents and young adults in England 1979–1997. *Br J Cancer* 2002;87:1267–74.
23 Ansell SM. Hodgkin lymphoma: 2012 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2012;87:1096–103.
24 Smith MA, Seibel NL, Altekruse SF, *et al*. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J Clin Oncol* 2010;28:2625–34.
25 NCIN. National Registry of Childhood Tumours Progress Report, 2012 Online www.ncin.org.uk/publications/ (accessed April 12 2013).
26 Hudson MM, Krasin M, Link MP, *et al*. Risk-adapted, combined-modality therapy with VAMP/COP and response-based, involved-field radiation for unfavorable pediatric Hodgkin's disease. *J Clin Oncol* 2004;22:4541–50.
27 Cashen AF, Bartlett NL. Therapy of relapsed Hodgkin lymphoma. *Blood Rev* 2007;21:233–43.
28 Ferrer R. Lymphadenopathy: differential diagnosis and evaluation. *Am Fam Physician* 1998;58:1313–20.
29 Townsend W, Linch D. Hodgkin's lymphoma in adults. *Lancet* 2012;380:836–47.

## Answers to the multiple choice questions

(1) D. (2) C. (3) B. (4) D. (5) B.

# Lymphadenopathy in children: refer or reassure?

David King, Jagadeesh Ramachandra and Daniel Yeomanson

*Arch Dis Child Educ Pract Ed* 2014 99: 101-110 originally published online January 2, 2014
doi: 10.1136/archdischild-2013-304443