

THE PROBLEM OF HIV-RELATED LYMPHADENOPATHY

Lymphadenopathy is a common condition in patients with HIV infection.

WILANDI JACOBS, MB ChB, MMed (Surg)

Surgeon in private practice, Northern Cape Province

Wilandi Jacobs obtained the MB ChB and MMed (Surg) degrees at the University of the Free State. She was then employed by the SAMS for a number of years. She now runs a successful private practice in the Northern Cape Province.

Correspondence to: W Jacobs (wilandijacobs@gmail.com)

As the prevalence of the human immunodeficiency virus (HIV) increases worldwide, the number of patients presenting to GPs and health care personnel with associated disease is increasing. Lymphadenopathy is a common presenting condition, with many potential interventions and pitfalls.

The concerns/problems with lymph nodes are essentially the following:

- It is a common presentation in HIV-positive patients early in the seroconversion phase through to end-stage disease.
- It is imperative not to miss a treatable or potentially treatable cause for the lymphadenopathy.
- If one were to perform a lymph node biopsy on every patient it would be impractical and costly and submit many patients to an unnecessary procedure.

However, the 'gold standard' for diagnosing the cause of the lymph nodes and excluding serious pathology still remains open biopsy. It is against this background that all other investigations in the HIV-positive population must be measured.

There are approximately 600 lymph nodes in the normal human body. Lymph nodes, including the spleen, adenoids, Peyer's patches and tonsils, are highly organised collections of immune cells that filter antigens from the extracellular fluid. The sinuses have a large number of macrophages, which remove approximately 99% of all antigens that cross lymph nodes.

Epidemiology of lymphadenopathy

Race

Race is not a factor in lymphadenopathy, but rare causes may be associated with particular racial groups, e.g. sarcoidosis in blacks and Kikuchi fujimora in Asians.

Gender

Gender does not influence lymphadenopathy.

Age

Lymphadenopathy is more common in young children as they are exposed to new infections/antigens. One-third of neonates and infants may have lymphadenopathy. Generalised lymphadenopathy is rare in the neonate and would suggest a congenital infection, e.g. cytomegalovirus.

Which nodes to investigate

This question is fundamental in the management of HIV lymphadenopathy.

In the following cases nodes need to be further investigated or treated:¹

- rapid enlargement of a previously stable node
- group of enlarged nodes, i.e. not generalised
- nodes with abnormal consistency
- tender nodes
- fluctuant nodes
- asymmetrical nodes

- nodes adherent to surrounding tissues
- nodes accompanied by other systemic symptoms.

Lymphadenopathy is a common presentation with many potential interventions and pitfalls.

Definition

Lymphadenopathy is normally classified as generalised (occurring in multiple nodal basins throughout the body) or localised (occurring in a single nodal basin) and is characterised by lymph nodes greater than 1 cm in diameter.

Persistent generalised lymphadenopathy (PGL) has one major cause, i.e. persistent follicular hyperplasia from chronic HIV infection. PGL requires no treatment if the lymph nodes remain stable in number, location and size.

The definition of PGL must include the following:²

- lymph nodes remain stable in number, location and size
- appropriate investigations reveal no cause
- lymph nodes are less than 2 cm in size
- two or more non-contiguous sites
- persists for more than 3 months.

In normal individuals without pathological disease axillary, inguinal and submandibular glands may be palpated.

History³

In a patient presenting with lymphadenopathy the following points should be noted in the patient's file:

- whether the lymph nodes are new
- whether they are progressing, i.e. enlarging
- whether they are persistent
- presence of constitutional symptoms, e.g. fever, sweats, fatigue and weight loss
- presence of localised pathology, e.g. axillary nodes in a patient with a breast mass
- full systemic history
- review of previous results, e.g. HIV serostatus, CD4 count, viral load
- medications – current or previous (see Annexure 1)
- history of trauma
- history of TB contact/exposure
- history of sexual behaviour
- history of risk-taking behaviours
- exposure to household pets.

Examination

- Vital signs should be recorded.
- Complete examination of all lymph node basins should be done.
- Documentation should include:
 - Location – may be helpful in narrowing the differential diagnosis, e.g. cat scratch disease typically causes cervical or axillary lymphadenopathy.

- Size – generally, nodes less than 1 cm are considered normal. However, epitrochlear nodes larger than 0.5 cm or inguinal nodes larger than 1.5 cm should be considered abnormal. The size of the node has no bearing on the specific diagnosis. An abnormal chest radiograph and lymph nodes greater than 2 cm in children are predictive of granulomatous disease or cancer (predominantly lymphomas).
- Consistency – very hard nodes are typical of malignancy, while firm, rubbery nodes suggest lymphoma. Softer nodes are usually caused by infective or inflammatory conditions. Shotty nodes typically have a viral aetiology and suppurant nodes may be fluctuant.
- Mobility – nodes that seem attached and move as a unit are usually referred to as matted and can be benign or malignant.
- Presence/absence of tenderness – when the capsule of a node stretches, it results in pain. This stretching is usually caused by inflammation, with suppuration or haemorrhage into a necrotic centre of a malignant node. Pain is not an accurate determinant of a benign or malignant condition.
- If a node is localised, the area/areas drained by that node should be carefully examined, e.g. cervicoaxillary – examine the breast and head and neck area.
- A full systemic examination should be done, focusing on hepatomegaly and the respiratory and genitourinary systems.

One-third of neonates and infants may have lymphadenopathy.

Areas of particular interest*

Cervical lymph nodes

- Cervical lymphadenopathy is common in children.
- Cervical nodes drain the tongue, external ear, parotid gland and deep structures of the neck.
- Lymph nodes posterior to the sternocleidomastoid (posterior triangle) are more ominous and carry a high risk of serious underlying disease, e.g. malignancy.
- Cervical lymphadenopathy may be caused by infection.

Submental and submandibular lymph nodes

- These nodes drain the teeth, tongue and buccal mucosa.
- They require thorough examination of the oral cavity.
- They may require referral to a dentist.
- Submental and submandibular lymphadenopathy is usually caused by localised infections such as pharyngitis, gingivitis and dental abscesses.

Occipital lymph nodes

- Occipital nodes drain the posterior scalp.
- They may be palpable in 5% of healthy children.
- Common causes are tinea capitis, seborrhoeic dermatitis, insect bites and orbital cellulitis.
- Viral causes include rubella and roseola infantum.

Peri-auricular lymph nodes

- These nodes drain the conjunctiva, eyelids, temporal region of the scalp and skin of the cheek.
- Thorough examination of the eye to exclude conjunctivitis, corneal ulceration and eyelid infections should be done.

Mediastinal lymph nodes

- These nodes drain the thoracic viscera.
- They are not detected on physical examination, but by radiological investigations.
- Mediastinal nodes may cause cough, wheezing, dysphagia, haemoptysis, atelectasis and superior vena cava syndrome – an indication for urgent referral to a specialist.

Supraclavicular lymph nodes

- These nodes drain the head, neck, arms, superficial thorax, lungs, mediastinum and abdomen.
- Left supraclavicular nodes (Virchow-Trosier's nodes) reflect intra-abdominal drainage, especially when there are no other lymph nodes in the cervical region.
- Right-sided supraclavicular nodes typically enlarge in the case of intra-thoracic lesions.

Axillary lymph nodes

- These nodes drain the hand, arm, lateral chest, abdominal wall and breast.
- In patients with a high risk of breast carcinoma, mammography may be warranted.
- These nodes may occur after immunisation.
- Hydradenitis suppurativa may be a cause of axillary lymph nodes.

Abdominal lymph nodes

- These nodes drain the pelvis, lower extremities and abdominal organs.
- They are not readily discernible on clinical examination.
- They may present with abdominal pain, backache, increased urinary frequency, constipation or bowel obstruction secondary to intussusception.
- Mesenteric adenitis may have a viral aetiology, but may also be confused with appendicitis.
- Mesenteric adenopathy may also be caused by neoplasms, typically Hodgkin's disease and non-Hodgkin's lymphoma.

Iliac and inguinal lymph nodes

- These nodes drain the lower limbs, perineum, buttocks, genitalia and lower abdominal wall.
- They are considered pathological if greater than 1.5 cm in diameter.
- These nodes are typically caused by infections.
- A full genital and anal examination is warranted.

Persistent generalised lymphadenopathy (PGL) has one major cause, i.e. persistent follicular hyperplasia from chronic HIV infection.

Investigations⁵

All investigations should be tailored to the patient's presenting complaints and to what was found on systemic examination, including any of the following not directly related to the lymph node:

- CD4 count
- HIV viral load
- full blood count
- liver function test
- chest radiograph
- sputum for TB/acid-fast bacilli
- test for sexually transmitted disease, e.g. rapid plasma reagin test
- blood cultures
- evaluation of renal function and urinalysis
- ultrasonography.

Biopsy

Before a biopsy is done, treatment with antibiotics (covering bacterial pathogens frequently implicated in lymphadenitis) and re-evaluation in 2 - 4 weeks is a reasonable management option. The major question in HIV lymphadenopathy remains, i.e. which patients should be observed, which patients should undergo fine needle aspiration (FNA),⁶ and in which patients an open biopsy should be done. As already stated, histology (as opposed to cytology) remains the gold standard in diagnosing the aetiology of lymphadenopathy. However, obtaining tissue for histology either by core needle biopsy (CNB) or entire lymph node excision carries associated risks. The risks associated with CNB are possible injury to neurovascular bundles and pain. The quantity of the tissue obtained is limited and sampling error may occur.

If a biopsy is considered, the largest and most abnormal node (not necessarily the most easily accessible node) should be excised. Inguinal and axillary nodes are not suitable for biopsy as they often show reactive hyperplasia. In the setting of generalised

HIV-related lymphadenopathy

Lymphadenopathy lymph node biopsy should be avoided, as it is most likely of viral origin and can lead the pathologist to making the erroneous diagnosis of malignancy.

FNA often does not lead to a diagnosis because of non-representative samples, inability to evaluate the architecture of the entire node and the small amount of tissue/cells obtained. In addition, there is a small but discernible risk of sinus tract formation depending on the underlying pathology.

Any tissue obtained is a golden opportunity for management of these patients, and therefore tissue should be sent for:

- histopathology (submitted in formalin)
- bacterial cultures (submitted in saline)
- mycobacterial cultures
- fungal cultures.

In one study, excisional biopsies yielded a definitive diagnosis in only 40 - 60% of patients for 4 main reasons:

- inadequate specimen size
- improper handling
- node sampling error
- tissue sent for incorrect test.

Inguinal nodes typically show architectural distortion owing to chronic infections.

Pain is not an accurate determinant of a benign or malignant condition.

Causes of generalised lymphadenopathy

In a Dutch study it was noted that of the 2 556 patients seen in a general practice, only 256 (approximately 10%) were referred to a specialist. Of these, only 82 (3.2%) required a biopsy and only 1.1% were diagnosed with malignancy. The conclusion remains that the vast majority of lymphadenopathies are due to a benign infective cause. However, it should also be noted that these patients still require treatment for infective/non-neoplastic causes.

HIV-positive patients represent a distinct group for various reasons:

- Is the generalised lymphadenopathy due to HIV?
- Is the lymphadenopathy due to an HIV-related disease?
- Is the lymphadenopathy unrelated to the HIV?

Annexure 1 lists the causes of lymphadenopathy. This list is by no means complete but represents the most common causes of lymphadenopathy in the HIV/AIDS population.

Annexure 1. Causes of generalised lymphadenopathy

Medications that may cause lymphadenopathy:⁷

Allopurinol
Atenolol
Captopril
Carbamazepine
Cephalosporins
Gold
Hydralazine
Penicillin
Phenytoin
Primidone
Pyrimethamine
Quinidine
Sulfonamides
Sulindac

Causes of infection

HIV infection, including persistent generalised lymphadenopathy
Mononucleosis, Epstein-Barr virus
Mycobacterium avium complex
Tuberculosis (TB)
Cytomegalovirus
Secondary syphilis
Toxoplasmosis
Histoplasmosis and other fungal infections
Bartonella infection (bacillary angiomatosis)
Hepatitis B
Lyme disease
Chlamydia (lymphogranuloma venereum)
Widespread skin infections
Immune reconstitution inflammatory syndrome (IRIS)
Follicular hyperplasia

Localised lymphadenopathy

Any of the above

Infectious causes

Oropharyngeal and dental infections
Cellulitis or abscesses
Chancroid
TB (scrofula)

Neoplastic causes

Lymphoma
Acute and chronic lymphocytic leukaemias
Other malignancies and metastatic cancers
Kaposi's sarcoma

Other causes

Reactive process – benign
Sarcoidosis
Hypersensitivity reactions to medication
Serum illness
Rheumatoid arthritis
Castleman's disease

IN A NUTSHELL

- Lymphadenopathy is a common presenting symptom of HIV infection.
- The fundamental goal is to exclude malignancy or serious treatable causes.
- Lymphadenopathy in HIV-positive patients requires a full history, an examination and a determination of the cause.
- Special investigations should be tailored to what is suspected on history and examination.
- It is of fundamental importance to determine which patients need further investigation.
- Location, size, consistency, mobility and presence or absence of tenderness are important.
- Knowledge of the lymph node drainage area and the causes is essential.

References available at www.cmej.org.za