Topics in Primary Care Medicine

An Approach to Peripheral Lymphadenopathy in Adult Patients

GRETCHEN KUNITZ, MD, *San Francisco*

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Practicing internists or general practitioners are frequently faced with the task of evaluating an adult patient with peripheral lymphadenopathy. Peripheral adenopathy, by definition, is detectable by palpation. Lymph nodes in the mediastinum or retroperitoneum are central rather than peripheral and will not be discussed in this review. Whether regional or generalized, adenopathy may be the presenting complaint of patients with a wide variety of underlying illnesses. Although many of these illnesses are self-limited or easily treated, the incidence of lymphatic malignancy increases steadily with age. Retrospective reviews of peripheral lymph node biopsies in patients younger than 25 years of age repeatedly have shown a less than 20% incidence of malignancy. In contrast, in the over-50 age group, 55% to 80% of biopsies have shown a malignant process due to either primary lymphoma or metastatic carcinoma.

When a patient initially complains of localized or generalized swelling or when a practitioner first discovers presumptive adenopathy, the following questions must be asked: Is the swelling adenopathy? If adenopathy is present, what is the likelihood that malignancy is present? What diagnostic tests are indicated? Is biopsy necessary and, if so, when should it be done? The answers to these questions will vary considerably among patients. A thorough review of patient characteristics such as age and duration and severity of symptoms combined with an assessment of the character and location of the adenopathy will aid practitioners in their evaluation and diagnostic plan. The intent of this review is to provide a framework for diagnostic evaluation.

Is the Swelling Adenopathy?

On initial evaluation it is often difficult to distinguish actual adenopathy from swelling due to other causes. Neck cellulitis, periodontal abscess, thyroglossal duct cyst or parotitis may mimic cervical adenopathy. Similarly, an inguinal hernia or enlarged axillary sweat gland may be mistakenly identified as an enlarged node.

Determining the Likelihood of Malignancy

As a working definition, it is useful to consider the presence of one or more nodes greater than 1 cm in size or multiple smaller nodes as grounds for further investigation. In addition to evaluating lymph node *size*, the *character* of the adenopathy must be evaluated. Although tender nodes are often indicative of an infectious process and rock-hard or rubbery nodes suggestive of malignancy, these axioms should serve as guidelines rather than as absolute rules. The *location* of the node is of diagnostic importance, as malignant tumors are most commonly found in cervical and supraclavicular sites. Isolated inguinal adenopathy is rarely associated with malignancy. Also important are the *duration* and *rate of growth* of the adenopathy. Steadily enlarging nodes over a period of months are more suspicious than newly discovered nodes that change little in size in the initial weeks of evaluation. Once the characteristics of the nodes have been evaluated, the characteristics of the patient need careful consideration. Bacterial infection accounts for 75% to 85% of adenopathy in the pediatric age group. Thus, a 10-year-old who presents with a tender, enlarged cervical node initially requires aspiration for culture rather than excisional biopsy. In a recent retrospective study of 123 patients in the 9- to 25-year age group undergoing lymph node biopsy, lymph node size greater than 2 cm or an abnormal chest radiograph correlated with the finding of granuloma or tumor at biopsy (or, in some cases, both). A history of ear, nose or throat symptoms correlated with the absence of these biopsy findings. Discriminate analysis

(Kunitz G: An approach to peripheral lymphadenopathy in adult patients [Topics in Primary Care Medicine]. West J Med 1985 Sep; 143:393-396)

From the Division of General Internal Medicine, Department of Medicine, San Francisco General Hospital Medical Center and University of California, San Francisco, School of Medicine.

Reprint requests to Gretchen Kunitz, MD, San Francisco General Hospital Medical Center, Dept of Medicine (5H22), 1001 Potrero Ave, San Francisco, CA 94110.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
EBV = Epstein-Barr virus

showed a wide range of other symptoms and signs to be unhelpful in predicting which biopsy specimens would show a granulomatous or malignant process. In an older adolescent or adult patient, an assessment based on patient and nodal characteristics is required. Reviewing the major causes of adenopathy by region will aid in formulating a diagnostic plan.

Cervical Adenopathy

Of the hundreds of lymph nodes composing the lymphatic system, the cervical nodes are most often noted by both the patient and practitioner to be enlarged. The most common cause of cervical adenopathy is bacterial or viral infection of the face or oropharynx. A careful examination of the throat and mouth may show the primary source of infection, thus mitigating the need for further evaluation.

With the recent influx of immigrants from South America and Southeast Asia, the incidence of tuberculosis in the United States has increased. Cervical adenopathy may be the presenting complaint of patients infected with *Mycobacterium tuberculosis*.

The common house cat is the definitive host of the protozoan intracellular parasite causing toxoplasmosis. Following contact with cat feces, a cervical or generalized adenopathy may develop. Although usually asymptomatic, this adenopathy occasionally is associated with low-grade fever, malaise and hepatosplenomegaly. The diagnosis rests on detecting serum IgM antibodies. A titer of greater than 1:80 or a fourfold or greater rise in paired serum specimens establishes the diagnosis.

Infectious mononucleosis caused by the Epstein-Barr virus (EBV) is an acute self-limited illness of young adults. It is characterized by fever, pharyngitis, splenomegaly and posterior cervical adenopathy. The adenopathy may persist for many weeks and typically the nodes are firm and tender to palpation. A physician who conducts a superficial examination of a patient with mononucleosis erroneously may prescribe antibiotic therapy for a presumptive bacterial pharyngitis. In as many as 80% of patients with mononucleosis a maculopapular skin rash develops when they are treated with ampicillin. The diagnosis of mononucleosis rests on recording a leukocytosis with increased numbers of atypical lymphocytes in conjunction with a positive heterophil antibody or Monospot slide test. Of these two tests, the Monospot is both more sensitive and more specific.

A clinical syndrome similar to mononucleosis is associated with cytomegalovirus. The adenopathy and pharyngitis associated with this illness are less pronounced than those associated with EBV. The diagnosis is confirmed by recording a fourfold rise in complement-fixing titers or by cytologic examination of a tissue or urine specimen for cytomegalic cells with intranuclear inclusions. Patients with this syndrome are heterophil antibody-negative.

Various malignant conditions may present with localized cervical adenopathy. Although this occurs most commonly with Hodgkin's disease, it may also occur with other lymphomas or leukemias or, rarely, with thyroid or nasopharyngeal carcinomas.

Preauricular and Postauricular Adenopathy

The differential diagnosis of isolated preauricular and postauricular adenopathy is limited to several common infections. Bacterial or viral conjunctivitis and infections of the eyelid or sinus tracts may result in painful enlargement of the preauricular nodes. Before the widespread use of rubella vaccine in the United States, postauricular adenopathy was commonly seen. The adenopathy may occur as early as a week before the appearance of the typical rash. The diagnosis is confirmed by recording a fourfold rise in serologic titers. The other major causes of postauricular adenopathy are infections of the scalp or ear and postauricular sinus tracts.

Supraclavicular Adenopathy

Most enlarged supraclavicular nodes are associated with malignancy. The left supraclavicular node (Virchow's or sentinel node) drains the lymphatic system of the abdomen, kidney and pelvis, whereas the right-sided node drains the mediastinum, lungs and esophagus. Because they lie behind the clavicular head of the sternocleidomastoid muscle, these nodes often go undetected on routine physical examinations. Asking a patient to do a Valsalva maneuver may facilitate detection.

Axillary Adenopathy

Axillary adenopathy is most commonly associated with bacterial infections of the upper extremity and cancers of the breast. *Mycobacterium marinum* (fishtank granuloma) and sporotrichosis are uncommon causes of axillary adenopathy. Another cause of axillary adenopathy is cat-scratch disease, a usually benign, self-limited illness thought to be caused by a pleomorphic Gram-negative bacterium. The adenopathy appears within one to two weeks of the initial scratch and may persist for months. Associated fever, malaise, myalgias or encephalitis are rare. As there are no serologic tests to document infection with cat-scratch disease, this remains a diagnosis of exclusion. Brucellosis, sporotrichosis and, in rare instances, non-Hodgkin's lymphoma also may present with isolated axillary adenopathy.

Inguinal Adenopathy

It is useful to separate the causes of inguinal adenopathy into sexually and nonsexually transmitted cases (Table 1).

Sexually transmitted diseases. In urban general medical practice, most cases of inguinal adenopathy are caused by the sexually transmitted diseases of syphilis, herpes simplex, gonorrhea, chancroid, lymphogranuloma venereum and granuloma inguinale.

TABLE 1.—*Causes of Inguinal Adenopathy*

Sexually Transmitted Diseases	*Nonsexually Transmitted Diseases*
Syphilis	Lower extremity infection
Herpes simplex	Cat-scratch disease
Gonorrhea	Bubonic plague
Chancroid	Tularemia
Lymphogranuloma venereum	Lymphoma
Granuloma inguinale	Pelvic malignancy

The primary chancre of syphilis develops three to four weeks after exposure to *Treponema pallidum*. Bilateral inguinal adenopathy develops in 50% to 70% of patients about a week after appearance of the chancre. The nodes typically are nontender and firm and in women may be absent if only the deep inguinal system is affected. This regional adenopathy of primary syphilis must be distinguished from the generalized adenopathy of secondary lues, occurring two to ten weeks postchancre. Diagnosis rests on darkfield examination of the primary lesion or on positive serologic tests.

The initial genital infection with herpes simplex type 2 invariably presents with vesicular eruptions and painful bilateral inguinal adenopathy. The adenopathy may persist for as long as six weeks after the initial infection. Recurrent outbreaks of genital herpes are associated with variable degrees of adenopathy.

Gonococcal urethritis may be associated with painful bilateral inguinal adenopathy, but, more commonly, no adenopathy is present. The painful adenopathy seen in conjunction with chancroid infection is unilateral, occurring simultaneously with, or shortly after, the appearance of a genital ulcer. Suppuration occurs in as many as 50% of infected patients. Diagnosis rests on finding Gram-negative bacteria or by tissue culture of the organism, *Hemophilus ducreyi*.

Lymphogranuloma venereum infection, caused by *Chlamydia trachomatis*, frequently presents with painful inguinal adenopathy two to six weeks after exposure. The genital chancre often goes unnoticed and the patient seeks medical attention because of the adenopathy. In 70% of cases, the adenopathy is unilateral. In men, a large painful bubo grooved by the inguinal ligament (inguinal groove sign) may develop. This rarely occurs in women. Concurrent proctitis, rectal abscess or fistula may be seen, and in 5% of patients chronic adenopathy develops.

The inguinal adenopathy seen in conjunction with granuloma inguinale is typically a chronic indolent enlargement caused by deposition of subcutaneous granulation tissue. Diagnosis rests on histologically documenting Donovan bodies and granulation tissue.

Nonsexually transmitted diseases. Infections of the lower extremity may cause inguinal adenopathy and should be carefully looked for during the physical examination. From 10% to 25% of patients with cat-scratch disease present with inguinal adenopathy, presumably due to a prior cat scratch in the lower extremity. Similarly, a bite to the lower extremity by a flea infected with *Yersinia pestis* results in bubonic plague, which is also associated with a unilateral inflammatory adenopathy. Although an uncommon disease affecting from 2 to 20 Americans yearly, mortality approaches 50% to 90% in the untreated patients. Cultures of nodal aspirate and blood specimens are essential for an early diagnosis. Tularemia is associated with an ulcerated painless papule at the site of inoculation, followed by tender regional adenopathy. The incidence of tularemia has increased steadily since 1975, with 200 to 300 cases reported yearly in the United States. In rare cases, lymphoma may present with isolated inguinal adenopathy.

Generalized Adenopathy

While a comprehensive discussion of generalized lymphadenopathy is beyond the scope of this review, the differential diagnosis is presented in Table 2 and is usefully divided into infectious causes, malignant tumors, collagen vascular diseases, dermopathies and hypersensitivity reactions, which are commonly drug-induced. Among gay men and intravenous drug users, generalized adenopathy may herald the onset of the acquired immunodeficiency syndrome. In rare cases, sarcoidosis, hyperthyroidism or the lipid storage diseases may result in general adenopathy.

TABLE 2.—*Differential Diagnoses for Generalized Lymphadenopathy*

Infections	Bacteremia, miliary tuberculosis, brucellosis, leptospirosis, syphilis, tularemia, histoplasmosis, sporotrichosis, mononucleosis, typhoid, leprosy, viral syndromes
Malignancy	Myeloproliferative, lymphoproliferative
Inflammatory	Lupus erythematosus, rheumatoid arthritis
Metabolic	Hyperthyroidism, lipidoses
Dermopathic	Eczema, skin rash
Other	Angioimmunoblastic reactions, phenytoin (Dilantin) hypersensitivity, acquired immunodeficiency syndrome or related condition, sarcoidosis

When working up a patient with diffuse adenopathy, the practitioner should take a medical history that includes sexual preference, occupational and travel history, use of drugs and a complete review of systems. In conjunction with a meticulous physical examination, the lengthy list of causes of generalized adenopathy can usually be narrowed considerably.

Use of Diagnostic Tests

A logical approach to a diagnostic evaluation must take into account salient features of each patient's history combined with the clinical features of adenopathy. As it is neither cost-efficient nor acceptable to patients to do an exhaustive evaluation at the first discovery of adenopathy, the practitioner must determine the extent and rapidity of diagnostic testing to use in each individual case.

In 1978 Greenfield and Jordan developed an algorithm for the investigation of lymphadenopathy. They recommended an initial search for infectious processes, reserving biopsy for those patients with prominent systemic symptoms or adenopathy persisting for more than a week (in the absence of documented infection or drug reaction). This algorithm serves as a useful starting point in evaluating the case of an adult or adolescent patient with lymphadenopathy.

The initial laboratory evaluation in all patients should include a complete blood count. Elevations of the sedimentation rate or hepatic aminotransferase or alkaline phosphatase levels may be present in a patient with lymphoma or metastatic carcinoma, but these tests are nonspecific. A chest radiograph is often useful in that 20% of patients with lymphomas will show abnormalities, as will patients with sarcoidosis, fungal disease or other malignant processes. Mammography is recommended in a woman who presents with axillary adenopathy.

A homosexual man or intravenous drug user with lymphadenopathy presents special problems. In 1981 when large numbers of cases of the acquired immunodeficiency syndrome (AIDS) were first recognized, lymphadenopathy was reported in nearly 50% of patients with Kaposi's sarcoma and 25% of patients with *Pneumocystis* pneumonia. It has subsequently been noted that male homosexuals (and intravenous

drug users and hemophiliacs) frequently have persistent generalized adenopathy. Although the adenopathy may be associated with both neoplastic and infectious conditions, the vast majority of these patients who have lymph node biopsy show a nonspecific pattern of lymphoid hyperplasia.

The exact incidence of generalized adenopathy in the male homosexual population is unknown and it is unclear what percentage of patients with adenopathy will progress to opportunistic infection or neoplasm. Of 200 male homosexual patients with adenopathy evaluated prospectively by Abrams and co-workers in San Francisco and followed for a mean of 28 months, AIDS has developed in 16 (8%) (D. I. Abrams, MD, oral communication, June 1985). Rates of progression noted by other observers have ranged from 1% to 19%. As of May 1985, of 1,100 patients followed nationally for a mean of 20 months, AIDS has developed in 111 (D. I. Abrams, MD, oral communication, June 1985). In the San Francisco cohort, oral candidiasis, infections with herpes zoster, peripheral cytopenia and elevation of the erythrocyte sedimentation rate were found with greater frequency in the cases eventually progressing to AIDS. Other routine laboratory values or clinical variables were not predictive of outcome.

Given these data, it seems reasonable to search for occult malignancy or infection in a homosexual man or intravenous drug abuser who has diffuse lymphadenopathy, hematologic abnormalities, elevated sedimentation rates, oral thrush or herpes zoster. A lymph node biopsy should be reserved for this subset of patients as the yield from biopsy of enlarged nodes in most homosexual men is likely to be low.

When to Do a Biopsy

If an infectious workup is nondiagnostic and the patient has a persistent or progressive adenopathy of unknown cause, a biopsy is indicated. Determining exactly when to proceed with a biopsy is often difficult. As cancers are most commonly found in cervical and supraclavicular nodes, it is reasonable to do an earlier biopsy in a patient with adenopathy localized to these sites. Examination of the ears, nose and throat should be done before a biopsy in a patient with prominent cervical nodes. A woman with prominent axillary adenopathy also warrants an early biopsy, as does an older patient with diffuse, firm adenopathy. Generally speaking, the presence of significant localized adenopathy of longer than two to three weeks' duration without a documented infectious cause is grounds for a biopsy in *all* patients, regardless of age. The presence of diffuse adenopathy in the absence of a known drug reaction, infection or rheumatologic disease also warrants a biopsy.

TABLE 3.—*Diagnostic Yield of Lymph Node Biopsy*

Biopsy Results	*Percent*
Diagnostic	50-63
Nondiagnostic	37-53
Children, excellent prognosis	...
Adults, disease will develop	25-50
lymphoma will develop	20
Problems in diagnosis include	
Poor choice of biopsy site	
Poor surgical technique	
Poor processing	
Poor interpretation	

A lymph node biopsy can be an extremely useful procedure. The internist, surgeon and pathologist should work closely from the outset to assure maximum yield. In several recent reviews the diagnostic yield from peripheral lymph node biopsy in adults has been shown to be 37% to 63% (Table 3). In patients whose initial biopsies are nondiagnostic, a repeat biopsy is often useful. From 25% to 50% of these patients will show evidence of disease on repeat biopsy and a substantial portion (20%) of this group will be diagnosed with lymphoma. The choice of the node from which a biopsy will be taken and the proper biopsy technique are crucial. Generally speaking, it is best to choose the largest accessible node. Ideally, the entire node can be dissected for delivery to the pathologist. If pus or caseation is present, smears and cultures for bacteria and fungi are indicated. Frozen sections help in the diagnosis of nonlymphomatous malignancy, whereas specially stained slides are required for the diagnosis of lymphoma.

GENERAL REFERENCES

Abrams D: Lymphadenopathy syndrome in male homosexuals. Adv Host Defense Mechanisms 1985; 5:75-97

Barton LL, Feigin RD: Childhood cervical lymphadenitis. J Pediatr 1974; 84:846-852

Greenfield S, Jordan MC: The clinical investigation of lymphadenopathy in primary care practice. JAMA 1978; 240:1388-1393

Murphy JF, Fred HL: Infectious lymphadenitis or lymphoma? Seven lessons. JAMA 1976; 235:742-743

Saltzstein SL: The fate of patients with non-diagnostic lymph node disorders. Surgery 1965; 58:659-662

Sinclair S, Beckman E, Ellman L: Biopsy of enlarged superficial lymph nodes. JAMA 1974; 228:602-603

Slap G, Brooks J, Schwartz S: When to perform biopsies of enlarged peripheral lymph nodes in young patients. JAMA 1984; 252:1321-1326