

Approach to the Patient with Lymphadenopathy

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Lymphadenopathy refers to one or more lymph nodes that are abnormal in size, consistency, or number. Lymphadenopathy can be due to a benign, self-limited process or may be a sign of a serious underlying disease. Infections, malignancy, and immunologic disorders account for most cases of lymphadenopathy (**Table 1**). This article reviews the diagnostic approach to the patient with localized or generalized lymphadenopathy and discusses common, important systemic illnesses that may cause generalized lymphadenopathy.

EVALUATION OF LYMPHADENOPATHY

Key factors to consider when evaluating a patient with lymphadenopathy include the age of the patient, location of the lymphadenopathy, associated symptoms, and the presence or absence of splenomegaly. Age is the most important consideration because it helps predict the likelihood of a benign versus malignant process. In patients younger than 30 years, lymphadenopathy is due to a benign underlying process approximately 80% of the time, while in individuals older than 50 years, it is due to a malignant process approximately 60% of the time.¹

The second most important consideration is whether the lymphadenopathy is localized or generalized (defined as detectable lymph nodes in 2 or more regions). In localized lymphadenopathy, the lymphatic drainage areas should be investigated for infection or malignancy. Evaluation of the patient with generalized lymphadenopathy should include a careful history that focuses on systemic signs and symptoms (eg, fever, chills, night sweats, weight loss, and pruritus),² a thorough physical examination, complete blood count, and chest radiograph. In the adult patient, especially those aged 50 years or older, generalized lymphadenopathy usually represents a serious systemic illness. Fever, weight loss, and night sweats may suggest tuberculosis or lymphoma. Special attention should be given to the presence or absence of splenomegaly because this find-

KEY FACTORS IN EVALUATION OF LYMPHADENOPATHY

- Age of patient
- Location of lymphadenopathy
- Systemic signs/symptoms
- Presence/absence of splenomegaly
- Size, consistency, tenderness, and fixation of lymph nodes
- History of exposures
- Drug history

ing makes a malignancy of hematologic origin more likely.³ A detailed drug history should be obtained.

The 3 major regions for lymph node examination are the head and neck, axilla, and inguinal regions. Lymph nodes should be examined for size, consistency, tenderness, warmth, and fixation. The pads of the fingers should be used for palpation while moving the skin over the underlying tissues in each area. In general, lymph nodes larger than 1.0 cm in diameter are considered abnormal.⁴ Tender, warm, erythematous nodes are likely to be associated with a local infectious process. Hard fixed nodes are highly suggestive of malignancy. Finally, rubbery mobile nodes are suggestive of lymphoma.

REGIONAL LYMPHADENOPATHY

Head and Neck

The head and neck is the most frequent site for lymphadenopathy. Nodes in this region should be examined in the following sequence: preauricular, posterior

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Table I. Causes of Lymphadenopathy

Infections

Localized infections: cellulitis, cat-scratch disease, abscess, pharyngitis

Zoonotic infections: *Yersinia pestis* (plague), *Francisella tularensis* (tularemia)

Mycobacterial: tuberculosis

Fungal: histoplasmosis, cryptococcosis, sporotrichosis

Viral: infectious mononucleosis, cytomegalovirus, HIV

Parasitic: toxoplasmosis

Malignancies

Hematologic: lymphoma, leukemia

Solid tumors

Cervical adenopathy: head and neck cancers

Supraclavicular adenopathy: thoracic and abdominal malignancies

Axillary adenopathy: breast cancer, melanoma

Inguinal adenopathy: squamous cell cancer, melanoma

Immunologic disorders

Connective tissue disorders

Serum sickness (drug reactions, hepatitis B, immunizations, exposure to animal serum)

Sarcoidosis

Miscellaneous

Castleman's disease (lymph node hyperplasia)

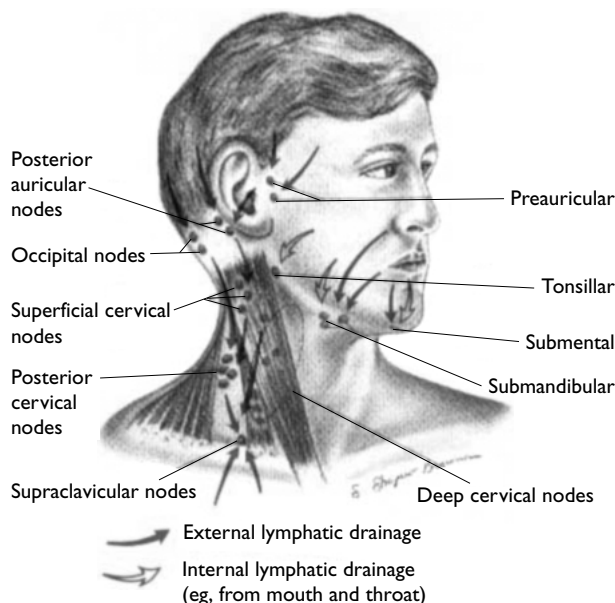


Figure 1. Lymph node distribution of the head and neck. (Reproduced from Bickley LS. Bates' guide to physical examination and history taking. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 1999:203. Copyright © 1999 by Lippincott Williams & Wilkins Philadelphia.)

auricular, occipital, tonsillar, submandibular, submental, superficial cervical, posterior cervical, deep cervical chain, and supraclavicular. The main cause of head and neck lymphadenopathy is infection, including bacterial pharyngitis, dental abscesses, otitis media and externa, toxoplasmosis, and viral infections such as cytomegalovirus and adenovirus. Malignant causes include Hodgkin's and non-Hodgkin's lymphoma, squamous cell carcinoma, and metastatic malignancies.^{5,6}

For lymphadenopathy of the head and neck, knowing the region drained by the involved lymph node can give clues to the underlying process (Figure 1). The preauricular and occipital nodes drain the head and may represent superficial skin infections, while the posterior auricular nodes drain the ear and may indicate an otitis externa or media. The tonsillar, submandibular, and submental lymph nodes drain the oral cavity soft tissues of the face. The superficial cervical nodes drain the tissues of the neck, while the deep cervical nodes drain the larynx, trachea, thyroid, and esophagus. The supraclavicular nodes receive drainage from the chest and mediastinum and on the left side receive drainage from the thoracic duct from the abdominal

lymphatics. Detection of an enlarged left-sided supraclavicular node (Virchow's node) is always a cause for concern as it may indicate the presence of an occult abdominal neoplasm.

Other causes of neck mass. Neck lumps can have benign or malignant causes. Neck lumps can generally be classified into 3 broad categories: inflammatory, congenital, and neoplastic. In a study evaluating 100 patients presenting with a neck lump, reactive (inflammatory) lymphadenopathy was the cause in half of the patients. The age of the patients ranged from 2 to 84 years, with the majority between 30 and 70 years. Other causes of neck mass in this cohort were salivary gland disorders (13), hematologic malignancies (12), lymph node metastasis (9), thyroglossal duct cysts (5), and branchial cleft cysts (4).⁷ Salivary gland disorders ranged from the benign sialadenitis to the malignant adenocarcinoma. Other benign causes included 2 lipomas and 2 sebaceous cysts. Ultrasonography may help differentiate cystic from solid masses, but fine-needle aspiration is definitive. Congenital cysts may also be differentiated based on their location. Thyroglossal duct cysts are centrally located, while branchial cleft cysts are laterally located. Because squamous cell carcinoma can sometimes mimic a branchial cleft cyst, fine-needle

aspiration may be necessary before excision if risk factors for malignancy are present.

Epitrochlear

Lymphadenopathy in this region most often results from repeated minor trauma and infections in manual laborers. In gardeners, sporotrichosis is a consideration. This infection is classically caused by traumatic inoculation with soil or organic matter contaminated with the fungus *Sporothrix schenckii*. Cat-scratch disease is also in the differential of epitrochlear lymphadenopathy. Cat-scratch disease is caused by *Bartonella henselae*, a gram-negative bacterium introduced by a scratch or bite of a cat. Physicians should look for lymphangitic streaking and signs of scratches or bites. Cat-scratch disease typically presents with an erythematous papule at the site of inoculation approximately 1 week after the trauma. Regional lymphadenopathy can present several days after the trauma.^{8,9} Not surprisingly, the 2 diseases can overlap as cats can transmit *Sporothrix* organism via a scratch.¹⁰ Epitrochlear lymphadenopathy may have a malignant etiology that includes lymphoma and chronic lymphocytic leukemia (CLL), but these malignancies are more likely to cause generalized lymphadenopathy.

Axillary and Inguinal

To palpate lymph nodes in the axilla, the patient should be in the seated position with arms flexed at the elbow (**Figure 2**). The patient's right axilla should be palpated with the left hand while the examiner supports the patient's right arm. The examiner's finger tips should roll the soft tissues of the axilla against the chest wall.

The axillary nodes drain the lymphatics of the upper extremity and the breasts. Common causes of axillary lymphadenopathy include staphylococcal and streptococcal infections, cat-scratch disease, tularemia, and sporotrichosis. Malignancies to consider include Hodgkin's disease, non-Hodgkin's lymphoma, breast carcinoma, and metastatic melanoma.

The inguinal lymph nodes drain the lower extremity, genitals, and perineum. Cellulitis and sexually transmitted diseases (eg, syphilis, chancroid, genital herpes, and lymphogranuloma venereum) are common causes of inguinal lymphadenopathy.¹¹ Lymphadenopathy is absent in granuloma inguinale, which is caused by *Calymmatobacterium granulomatis*. The characteristics of the genital lesion are helpful in distinguishing among the possible diagnoses (**Table 2**). Malignant conditions include lymphoma and metastatic squamous cell carcinoma and melanoma.

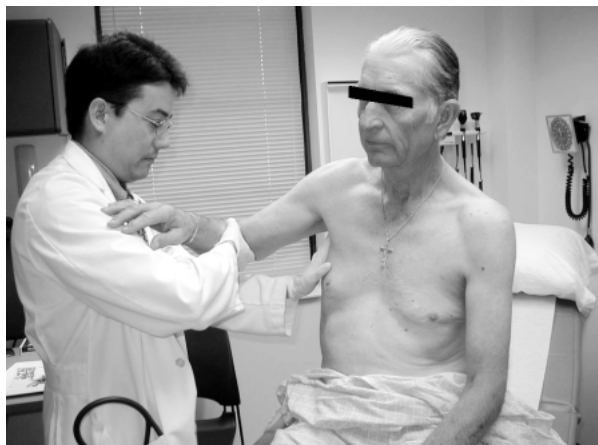


Figure 2. Palpation of axillary lymph nodes.

CAUSES OF GENERALIZED LYMPHADENOPATHY

Infectious Mononucleosis

More than half of patients with infectious mononucleosis manifest the triad of fever, lymphadenopathy, and pharyngitis. Examination of the throat will likely reveal enlarged tonsils. Streptococcal pharyngitis and other viral pharyngitides are other diagnostic considerations. A complete blood count with differential is essential as it may show a leukocytosis with atypical lymphocytes in a patient with infectious mononucleosis. Atypical lymphocytes are enlarged lymphocytes with increased cytoplasm with irregular edges and an irregular or indented nucleus (**Figure 3**).

Infectious mononucleosis can be confirmed by a positive heterophilic antibody test (human IgM antibodies that agglutinate sheep erythrocytes). The Monospot test is more commonly used.^{12,13} Acute cytomegalovirus infection and toxoplasmosis can cause a mononucleosis-like syndrome that includes many of the same features of mononucleosis, including a false-positive heterophile antibody test. Serologic tests that are helpful in differentiating these mimics of mononucleosis include IgM and IgG antibodies. A significant elevation in IgM titers of at least 30% of the IgG value is suggestive of cytomegalovirus or toxoplasmosis, while a negative IgM test essentially rules out an acute infection.^{14–16}

Serum Sickness

Serum sickness is a hypersensitivity reaction caused by exposure to foreign proteins or haptens which results in formation of immune complexes that are deposited in tissues and trigger an inflammatory response.¹⁷ Serum sickness is characterized by urticaria, facial edema, rash, lymphadenopathy, arthralgias, and fever. Products derived from animal serum, stings from

Table 2. Sexually Transmitted Diseases That Cause Inguinal Lymphadenopathy

Disorder or Disease	Characteristics of Genital Lesion	Organism
Primary syphilis (chancre)	Painless ulcer with indurated border	<i>Treponema pallidum</i>
Genital herpes	Cluster of shallow, small, painful vesicles/ulcers on a red base	Herpes simplex virus
Chancroid	Painful ulcer with sharp, undermined borders	<i>Haemophilus ducreyi</i>
Lymphogranuloma venereum	Painless papule, shallow erosion, or ulcer; may be multiple or single	<i>Chlamydia trachomatis</i>

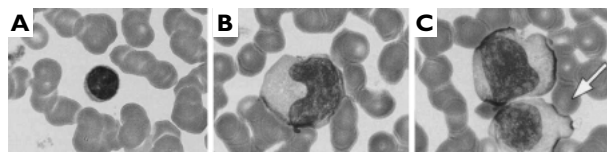


Figure 3. Normal and atypical lymphocytes of infectious mononucleosis. (A) Normal lymphocyte. (B) Atypical lymphocyte with irregular nucleus. (C) Atypical lymphocyte with irregular cytoplasmic shape. (Reprinted with permission from Auwaerter PG. Infectious mononucleosis in middle age. JAMA 1999;281:457. Copyright © 1999, American Medical Association. All rights reserved.)

Table 3. Differentiating the Leukemias

ALL*	Childhood leukemias (80%), adult leukemias (20%) Fatigue, easy bruising, lymphadenopathy, splenomegaly Pancytopenia (anemia, granulocytopenia, thrombocytopenia) Leukocyte count elevated ($> 100 \times 10^3/\mu\text{L}$)
AML	Median age, 45–55 years (80% of adult leukemias) Bruising, fever, lethargy, anemia, thrombocytopenia Causes: radiation, benzene, alkylating agents, myeloproliferative syndromes
CLL*	Median age, 60 years Stage 0 Lymphocytosis (prognosis 10 years) Stage 1 Lymphadenopathy Stage 2 Splenomegaly Stage 3 Anemia Stage 4 Thrombocytopenia (prognosis 1.5 years)
CML	Middle-aged adults Anemia, thrombocytosis, splenomegaly Elevated leukocyte count $> 150 \times 10^3/\mu\text{L}$ (chronic phase 2–4 years) Blast crisis (acute phase 2–6 months)

ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous leukemia.

*Note that the lymphocytic leukemias are more likely to present with lymphadenopathy.

insects, and several drug classes, including anticonvulsants and antibiotics, can cause serum sickness. As mentioned, it is important to obtain a detailed drug history. Phenytoin, carbamazepine, hydralazine, methyldopa, allopurinol, sulfas, and penicillins are common offenders. These hypersensitivity reactions occur within 2 to 6 weeks of initiating the drug and resolve within 2 to 3 weeks after drug discontinuation.

Hematologic Malignancies

Lymphomas. Lymphadenopathy associated with lymphoma may be located in the mediastinum without peripheral lymphadenopathy. Fever, night sweats, and unexplained weight loss of more than 10% of normal body weight constitute the “B symptoms” of lymphoma. These constitutional symptoms are less common in non-Hodgkin’s lymphoma than in Hodgkin’s disease. Enlarged lymph nodes are rubbery and painless and later become matted (matted nodes feel connected and move as a unit on palpation). Non-Hodgkin’s lymphoma generally presents with widespread lymphadenopathy, while Hodgkin’s lymphoma is characterized by its localized presentation with an orderly spread to contiguous nodal regions.

Acute leukemias. Acute lymphoblastic leukemia (ALL) is predominantly a childhood leukemia, while acute myelogenous leukemia (AML) typically presents in older individuals (Table 3). Patients with acute leukemias generally present with fatigue, fever, and bleeding. Physical examination reveals a pale patient with purpura and petechiae, lymphadenopathy, and splenomegaly. In ALL, lymphadenopathy and splenomegaly are more common. Lymphadenopathy is unusual in adult AML. Laboratory examination for the acute leukemias reveals pancytopenia with circulating blasts.

Chronic leukemias. CLL is predominantly a disease of older individuals, usually those age 50 years or older. Most patients with CLL are asymptomatic at presentation, while those who are symptomatic present with fatigue or lymphadenopathy. For the leukemias, peripheral lymphadenopathy tends to be associated

with the lymphocytic leukemias rather than the myelogenous leukemias. CLL usually follows an indolent course. Chronic myelogenous leukemia (CML) typically presents in middle age with fatigue, night sweats, and low-grade fever. Some patients complain of symptoms related to marked splenomegaly with left upper quadrant pain. Lymphadenopathy occurs as the disease accelerates. Rarely, CML patients will present with symptoms related to leukostasis with neurologic manifestations due to marked elevations of leukocytes.

Acute HIV Infection

Acute HIV infection affects numerous systems, including the lymphatics. The most common findings of acute HIV syndrome are fever, fatigue, rash, headache, and lymphadenopathy. Acute HIV infection can mimic other infectious diseases, including infectious mononucleosis, influenza, streptococcal pharyngitis, viral hepatitis, toxoplasmosis, and secondary syphilis.¹⁸ Primary HIV infection should be considered in any patient who presents with the findings and reports a history of risky behavior, such as unprotected sex or intravenous illicit drug use. Because the enzyme-linked immunosorbent assay and Western blot test used to diagnose HIV infection may not become positive until several weeks after the infection was acquired, viral RNA quantitation or the plasma p24 antigen test may be used instead.

WHEN TO BIOPSY

Lymphadenopathy from an infectious etiology can usually be diagnosed by means other than a biopsy. Biopsy is indicated when a malignant process is suspected. Fine-needle aspiration for cytology is usually sufficient to evaluate for metastatic malignancies, such as in the case of a supraclavicular Virchow's node when a metastatic intra-abdominal malignancy is possible. However, if a lymphoma is suspected, an excisional lymph node biopsy is indicated to evaluate nodal architecture.

CONCLUSION

Key factors to consider when evaluating a patient with lymphadenopathy include the age of the patient, location of the lymphadenopathy, and associated symptoms. Most cases of lymphadenopathy are due to infections, malignancy, and immunologic disorders. Lymphadenopathy is most likely due to a benign self-limited infectious process in younger individuals or may be a

sign of a serious underlying disease such as malignancy in older individuals. **HP**

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