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Evaluation and Management of Lymphadenopathy in Children

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Objectives After completing this article, readers should be able to:

1. Define lymphadenopathy.
2. Develop a systematic approach to the evaluation and management of lymphadenopathy.
3. Discuss the differential diagnosis of localized and generalized lymphadenopathy.
4. Recognize worrisome features of lymphadenopathy that should prompt a referral for a biopsy.

Introduction

Examining the lymph nodes is an important aspect of the general physical examination of both well and ill children and adolescents. Lymph nodes are normal structures, and certain lymph nodes may be palpable in a healthy patient, particularly in a young child. Conversely, the presence of abnormally enlarged lymph nodes ("lymphadenopathy") can be a clue to a serious underlying systemic disease, and the differential diagnosis of lymphadenopathy can be broad. Thus, the challenge for the general pediatrician is to learn how to distinguish pathologic from nonpathologic lymph nodes and to develop a rational approach to the evaluation of lymphadenopathy. Because of its association with malignancy, lymphadenopathy can be a major source of parental anxiety. Therefore, it is crucial to know when to provide reassurance and to recognize when concern is sufficient to warrant referral to a subspecialist.

A Review of the Lymphatic System

The lymphatic system is an open circulatory system that is a component of the immune system. It includes lymph, lymphatic vessels, lymph nodes, spleen, tonsils, adenoids, Peyer patches, and the thymus. Lymph contains lymphocytes and is an ultrafiltrate of blood that is collected in lymphatic capillaries present throughout the body in all organs except the brain and heart. Lymph moves slowly, without a central pump and under low pressure, via peristalsis and through the milking action of skeletal muscles. Lymph is transported from the head and extremities to progressively larger lymphatic vessels and ultimately into either the right lymphatic duct (lymph from the right upper body) or the thoracic duct (lymph from the rest of the body). These ducts ultimately drain into the venous system at the right and left subclavian veins. En route to the lymphatic and thoracic ducts, lymph traverses lymph nodes via afferent and efferent lymphatic vessels through a systematic drainage system. A working knowledge of the nodal basins and the anatomy of the regions they drain is helpful in formulating a differential diagnosis for lymphadenopathy (Table 1).

The body has approximately 600 lymph nodes. These are composed of follicles, some with germinal centers, and the various classes of lymphocytes (B cells and T cells) sequestered in particular areas of the node. In the nodes, lymph is filtered through sinuses, where particulate matter and infectious organisms are phagocytosed, processed, and presented as antigens to surrounding lymphocytes. Antibody production, T-cell responses, and cytokine production all occur in lymph nodes. Lymph nodes can enlarge by either proliferation of normal cells that comprise the lymph node or infiltration by foreign or abnormal cells.

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Table 1. **Lymphatic Drainage of the Body**

Lymph Node Group	Region Drained by Lymph Nodes
Head and Neck	
Occipital	Posterior scalp
Postauricular	Temporal and parietal scalp
Preauricular	Anterior and temporal scalp, anterior ear canal and pinna, conjunctiva
Parotid	Forehead and temporal scalp, midface, external ear canal, middle ear, gums, parotid gland
Submandibular	Cheek, nose, lips, tongue, submandibular gland, buccal mucosa
Submental	Lower lip, floor of mouth
Superficial cervical	Lower larynx, lower ear canal, parotid
Deep cervical	Tonsils, adenoids, posterior scalp and neck, tongue, larynx, thyroid, palate, nose, esophagus, paranasal sinuses
Supraclavicular	Right side: mediastinum, lungs
	Left side: abdomen
Deltopectoral	Arm
Axillary	Arm, breast, thorax, neck
Epitrochlear	Medial arm below elbow
Inguinal	Lower extremity, genitalia, buttocks, abdominal wall below umbilicus
Popliteal	Lower leg

Clinical Approach to Lymphadenopathy

The term "lymphadenopathy" refers to lymph nodes that are abnormal in size, number, or consistency. Lymphadenopathy may be part of a constellation of signs and symptoms or the sole finding and chief complaint. Formulating a differential diagnosis requires consideration of several important clinical features: 1) age of the patient, 2) size of the nodes, 3) location of the nodes, 4) quality of the nodes, 5) whether lymphadenopathy is localized or generalized, and 6) time course of the lymphadenopathy and other associated symptoms.
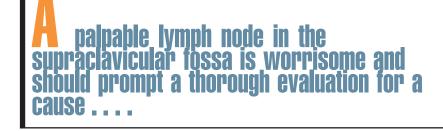
Patient Age

The age of the patient is important because the normal sizes of various lymph nodes change with age, as do the diagnoses that should be entertained. Lymph nodes generally are not palpable in the newborn. Over time and with antigenic exposure, the volume of lymph node tissue increases. Palpable lymph nodes in the cervical, axillary, and inguinal regions are normal throughout early childhood. "Shotty" lymphadenopathy is a term used to describe the finding of small mobile lymph nodes, so-called because of the resemblance to buckshot under the skin. This finding is very common in young children and generally is a benign condition, seen frequently in the setting of a viral illness. In a series of children younger than 5 years of age, 44% had palpable lymph nodes at the time of a health supervision visit, and 64% of children seen for sick visits had palpable lymph nodes. (1) Palpable lymph nodes were most common between the ages of 3 and 5 years.

The differential diagnosis of lymphadenopathy changes substantially with age. For example, Hodgkin lymphoma is an important cause of lymphadenopathy in the adolescent and adult patient population, but it is rare before 10 years of age. Thus, Hodgkin disease should be considered early in a teenager who seemingly is well but has a pathologically enlarged cervical or supraclavicular lymph node, whereas a 3-year-old child who has the same finding may be observed more reasonably for some appropriate period of time. Sexually transmitted diseases are a common cause of inguinal lymphadenopathy in late adolescence and adulthood. Conversely, upper respiratory tract infections, otitis, and conjunctivitis frequently lead to a nearly chronic reactive cervical lymphadenopathy in the preschool and early school age groups.

Congenital lesions that may be confused with lymphadenopathy and should be considered in the differential diagnosis of a neck mass in a young child include cystic hygroma, branchial cleft cyst, thyroglossal duct cyst, and cervical rib. A cystic hygroma is a proliferation of lymphatic vessels (a lymphangioma) that is soft and compressible and is palpable in the lower neck above the clavicle; it will transilluminate. Branchial cleft cysts are in the lateral neck and usually can be differentiated from lymphadenopathy by the presence of a pit, dimple, or sinus along the anterior margin of the sternocleidomastoid muscle. Such cysts can become infected, making them difficult to distinguish from cervical lymphadenitis. Thyroglossal duct cysts occur in the midline at the level of the thyrohyoid membrane and usually move up and

down with swallowing or protrusion of the tongue. A cervical rib has a different contour and a hard, bony consistency that distinguishes it from a lymph node.

Size of Lymph Nodes

Although defining "normal" and "abnormal" in terms of size can be challenging, a rule of thumb is as follows: Normal lymph nodes in the axillary and cervical regions are up to 1 cm in size, in the inguinal regions up to 1.5 cm in size, and in the epitrochlear location up to 0.5 cm in size. As mentioned, the size limits differ somewhat by age and generally are less stringent in young children than in adolescents and adults, presumably because of the frequent antigenic exposure in early childhood to common childhood illnesses and the gradual acquisition of antibodies and immunity. The risk of underlying malignancy increases with increasing size of the lymph node, with 2 cm in diameter seeming to be an important threshold for cervical nodes in children and a smaller threshold held for adults and older adolescents. (2)(3)

> ## A palpable lymph node in the supraclavicular fossa is worrisome and should prompt a thorough evaluation for a cause . . . .

Location of Lymph Nodes

As outlined in Table 1, the location of the abnormal lymph nodes can direct the clinician in a thorough search for potential sources of infection. Examples of this association include an enlarged axillary lymph node in the setting of cat-scratch disease from a scratch on the arm or anterior cervical lymphadenopathy related to pharyngitis. A palpable lymph node in the supraclavicular fossa is worrisome and should prompt a thorough evaluation for a cause, with malignancy high in the differential diagnosis, creating a low threshold for excisional biopsy. Inguinal and axillary lymph nodes generally are associated with a lower likelihood of disease.

Quality of Lymph Nodes

Tender lymphadenopathy most frequently is caused by infection, especially if there is associated erythema, warmth, induration, or fluctuance. Occasionally, malignancy can cause node tenderness because of hemorrhage

into the node and subsequent stretching of the capsule. Nodes that are soft, easily compressible, and freely mobile frequently are benign. Hard nodes are found in cancers that induce fibrosis and when previous inflammation has resulted in fibrosis. Lymphomatous nodes frequently are firm and rubbery. Nodes that become fixed or matted to each other usually result from invasive cancers or from inflammation in the tissue surrounding the nodes, as in tuberculosis or sarcoidosis.

Localized Versus Generalized Lymphadenopathy

It is useful to classify lymphadenopathy as either generalized, where two or more nodal groups or sites are involved, or localized to a single area. Localized lymphadenopathy is a more common presenting finding in a primary care practice than generalized lymphadenopathy, with the cervical lymph nodes being involved most commonly, followed by inguinal nodes. Localized adenopathy can occur from infection of the node itself (lymphadenitis) or from an infection in its drainage area. Generalized adenopathy is caused by systemic disease; other abnormal findings such as hepatosplenomegaly or rash are frequent. Table 2 provides a detailed list of causes of localized and generalized lymphadenopathy in a pediatric population and includes rare disorders that are not detailed in this review.

Time Course of the Lymphadenopathy and Other Associated Symptoms

When gathering a history, the clinician should ascertain the duration of the lymphadenopathy and whether there seems to have been progression in size or number. Many advocate biopsy of concerning nodes that have not decreased after 4 to 6 weeks or have not normalized completely in 8 to 12 weeks. On the other hand, lymph nodes that have been present for a very long duration are not likely to be malignant. One exception to this observation is Hodgkin disease, which tends to be rather indolent; a 6- to 12-month duration of lymphadenopathy before diagnosis is not uncommon. History also should focus on exposures (to animals, uncooked meats, unpasteurized milk), medications (some of which can cause lymphadenopathy), and associated constitutional symptoms such as fever, night sweats, weight loss, pruritus, arthralgias, or fatigue.

Table 2. Differential Diagnosis of Lymphadenopathy in the Pediatric Patient

Infections

Bacterial
  Localized:
    Staphylococcus aureus, group A *Streptococcus* (eg, pharyngitis), anaerobes (periodontal disease), cat-scratch disease, tularemia, bubonic plague, diphtheria, chancroid
  Generalized:
    Brucellosis, leptospirosis, lymphogranuloma venereum, typhoid fever
Viral
  Epstein-Barr virus, cytomegalovirus, herpes simplex virus, human immunodeficiency virus, hepatitis B, mumps, measles, rubella, dengue fever
Mycobacterial
  Tuberculosis, atypical mycobacteria
Fungal
  Coccidiomycosis, cryptococcosis, histoplasmosis
Protozoal
  Toxoplasmosis, leishmaniasis
Spirochetal
  Lyme disease, syphilis

Malignancy

Leukemia, lymphoma, metastasis from solid tumor

Immunologic

Angioimmunoblastic lymphadenopathy with dysproteinemia, autoimmune lymphoproliferative disease, chronic granulomatous disease, dermatomyositis, drug reaction, rheumatoid arthritis, hemophagocytic lymphohistiocytosis, Langerhans cell histiocytosis, serum sickness, systemic lupus erythematosus

Endocrine

Addison disease, hypothyroidism

Miscellaneous

Amyloidosis, Castleman disease, Churg-Strauss syndrome, inflammatory pseudotumor, Kawasaki disease, Kikuchi disease, lipid storage diseases, sarcoidosis

Specific Causes of Lymphadenopathy

After taking the history and performing a physical examination, the clinician should be able to formulate a relatively narrow differential diagnosis for lymphadenopathy and, when necessary, obtain laboratory or imaging tests to establish a cause. Following are the more common causes of lymphadenopathy in the pediatric age range and their clinical features.

Reactive Lymph Nodes

Reaction to an infection in the drainage area is the most common cause of localized enlarged lymph nodes in children. Common childhood illnesses such as pharyngitis, otitis media, and conjunctivitis frequently can be identified in an examination to explain cervical lymphadenopathy. "Oculoglandular syndrome" is the constella-

tion of conjunctivitis and an enlarged preauricular lymph node; "ulceroglandular syndrome" is the constellation of a skin lesion and regional lymphadenopathy. Examples of the latter include impetigo caused by staphylococcal or streptococcal infections, cat-scratch disease, Lyme disease, anthrax, and tularemia.

Lymphadenitis

Lymphadenitis is defined as inflamed, enlarged, tender lymph nodes. The most common offending organisms are *Staphylococcus aureus* and group A *Streptococcus.* Group B S*treptococcus* also can be a pathogen in a young infant as a manifestation of late-onset infection, although *S aureus* is more common. Together, staphylococcal and streptococcal species account for up to 80% of cases of acute cervical lymphadenitis. The submandibular nodes

are involved most often. Typically, the onset is acute, with development of tender, erythematous, warm lymph nodes in the cervical region that may be associated with fever and progress over a few days to fluctuation. The onset also may be associated with an upper respiratory tract infection, pharyngitis, or impetigo. Cultures should be obtained of any draining skin lesions or of pharyngeal exudate. Initial treatment consists of a first- or second-generation cephalosporin or dicloxacillin. Often, treatment can be initiated with an oral antibiotic, although infants and ill-appearing older children who have fluctuant nodes or associated cellulitis require hospitalization for treatment with intravenous antibiotics. Incision and drainage may be indicated for abscess formation, particularly in the setting of infection with *S aureus*. Ultrasonography can be useful to help identify an abscess that requires surgical intervention.

In the southwestern United States, particularly New Mexico, there are occasional cases of bubonic plague, an infection caused by *Yersinia pestis*.

Anaerobic organisms are important pathogens for acute cervical lymphadenitis in older children, in whom polymicrobial infection commonly occurs in the setting of dental or periodontal disease. A close examination of the oropharynx is always an important part of the evaluation of cervical lymphadenitis, and dental consultation may be indicated. Antibiotic choices in the case of suspected anaerobic infection include clindamycin and amoxicillin-clavulanic acid.

In the southwestern United States, particularly New Mexico, there are occasional cases of bubonic plague, an infection caused by *Yersinia pestis*. This organism is carried by infected rodents and their fleas. The pathognomonic sign is a very painful lymph node, termed a "bubo," that usually is swollen and hot to the touch. Associated symptoms are fever, headache, and extreme exhaustion. A progressive, potentially fatal illness can ensue rapidly with septicemia and pneumonia. Early antibiotic treatment with an agent such as streptomycin or gentamicin is necessary.

Kawasaki disease needs to be considered in young children who have acute unilateral cervical lymphadenitis, especially if associated with high fever, irritability,

rash, conjunctivitis, oral mucositis, and edema of the extremities. On occasion, cervical lymphadenopathy is the predominant and earliest manifestation of the disease.

More indolent causes of lymphadenitis include *Bartonella henselae* (cat-scratch disease), *Mycobacterium tuberculosis*, and atypical mycobacteria. With these infections, fluctuant lymph nodes may develop over weeks to months, and tenderness and signs of inflammation frequently are absent. The nontuberculous (atypical) mycobacterial infection generally is acquired from contact with the environment (eg, soil and water) rather than by person-to-person spread, as in tuberculosis. There are many different strains, with *M avium* complex and *M scrofulaceum* accounting for most cases of disease in children. Involved lymph nodes in the anterior superior cervical or submandibular regions can progress to matting and eventually spontaneous rupture, forming cutaneous sinus tracts. An older term for this entity is "scrofula." Although it can be challenging to distinguish this infection from tuberculous disease, a tuberculin skin test usually is weakly positive (5 to 15 mm of induration versus >15 mm in tuberculosis), a chest radiograph appears normal, and systemic signs and symptoms are absent. Ideally, the infecting strain is isolated and susceptibility testing performed after complete surgical excision while nodes are still firm and encapsulated; otherwise, chronic drainage may develop.

Infectious Mononucleosis

The signs and symptoms of infectious mononucleosis include fever, pharyngitis, and lymphadenopathy, characteristically with symmetric involvement of the posterior cervical nodes more than the anterior cervical. Nodes may be large and kidney-shaped and typically peak in size over the first week of illness, gradually subsiding over the next few weeks. Axillary and inguinal nodes also may be involved. Fatigue, malaise, splenomegaly, hepatitis, atypical lymphocytosis, and rash appearing after exposure to a penicillin are other common features of the illness. Cervical adenopathy may be severe enough to cause upper airway compromise. The most common cause of infectious mononucleosis is Epstein-Barr virus, although other organisms can cause a mononucleosis-type syndrome, including cytomegalovirus, toxoplasmosis, *Streptococcus*, hepatitis B, and human immunodeficiency virus (HIV). Diagnostic tests for mononucleosis include the

monospot test (or "heterophile antibody"), which often produces false-negative results early in the illness, particularly in children younger than 4 years of age. Specific serologic tests, most importantly, an elevated immunoglobulin M titer to viral capsid antigen (IgM-VCA), indicate acute infection.

Differential Diagnosis of Generalized Lymphadenopathy

Although less common than localized lymphadenopathy in a general pediatric practice, generalized lymphadenopathy can be a sign of a serious underlying systemic disease and warrants a careful history and physical examination. In addition to the systemic infections mentioned previously (eg, infectious mononucleosis and tuberculosis), primary infection with HIV is an important cause of generalized lymphadenopathy. The adenopathy during the acute symptomatic phase of HIV infection usually is nontender and occurs in the cervical, occipital, and axillary regions in the setting of fever and malaise. Enlarged lymph nodes typically persist beyond this phase while other symptoms of chronic infection develop. The major causes of noninfectious lymphadenopathy are medications, malignancy, and autoimmune disease.

Lymphadenopathy is part of the constellation of symptoms seen in serum sickness that includes fevers, arthralgias, malaise, pruritus, and rash, which may be urticarial. The lymphadenopathy typically is tender, and there is a history of exposure to an offending medication. The common culprits in pediatric practice are carbamazepine, cephalosporins, penicillins, phenytoin (which also may cause lymphadenopathy without serum sickness), and sulfonamides.

The most common childhood cancer is acute leukemia, in which generalized lymphadenopathy can be a prominent feature. The adenopathy usually is nontender and may be bulky and grow rapidly. Other physical findings may include pallor, bruising or petechiae, and hepatosplenomegaly. A complete blood count (CBC) is a simple, useful screen because there usually are cytopenias of multiple cell lines, although the total white blood cell count may be low, normal, or high at the time of diagnosis. Lymphomas can present with either generalized or localized lymphadenopathy; solid tumors such as neuroblastoma or rhabdomyosarcoma involve regional lymph nodes, if the nodes are involved at all.

Autoimmune diseases such as systemic lupus erythematosus, juvenile idiopathic arthritis, and dermatomyositis can cause generalized lymphadenopathy. In these settings, nodes are usually nontender and discrete and range in size from 0.5 cm to a few centimeters in the cervical, axillary, and inguinal regions.

Diagnostic Evaluation

Usually the history and physical examination reveal the cause of lymphadenopathy. When worrisome features suggest a serious underlying disease, laboratory tests, imaging, and biopsy may be indicated. Depending on the clinical scenario, useful laboratory tests include a CBC, erythrocyte sedimentation rate (ESR), lactate dehydrogenase concentration (which can be a marker for hematologic malignancy), Mantoux tuberculin skin test, monospot, and specific serologic tests for infectious agents. A chest radiograph also can be very helpful to look for mediastinal or hilar adenopathy and should be obtained prior to referral of a patient for a biopsy because the presence of an anterior mediastinal mass can be a contraindication to general anesthesia. Any symptoms referable to the chest (cough, dyspnea, orthopnea, chest pain) also should prompt a chest radiograph. Corticosteroids never should be administered without a definitive diagnosis because they can mask the diagnosis of leukemia or lymphoma and adversely affect prognosis.

In the case of localized cervical lymphadenopathy, an observation period of 3 to 4 weeks is reasonable if no features in the history or physical examination suggest malignancy. When bacterial lymphadenitis is suspected, empiric treatment with antibiotics such as a first- or second-generation cephalosporin should be initiated. If there is no response to oral antibiotics, a tuberculin skin test should be placed as part of the evaluation for atypical mycobacteria.

Referral for biopsy is appropriate if there is continued progression or lack of any regression within 4 weeks. Immediate biopsy should be sought in the case of an enlarged supraclavicular lymph node or for findings suggesting malignancy such as hard, fixed, or nontender nodes; the absence of related symptoms suggesting infection; fevers lasting longer than 1 week; night sweats; weight loss greater than 10%; abnormal findings on the CBC or chest radiograph; or elevated ESR. When biopsy is indicated, an open, excisional biopsy at a center that has experienced hematopathologists is optimal. The largest and most abnormal node should be biopsied; in general, inguinal and axillary lymph nodes are less likely to be diagnostic. The highest yield is obtained with a supraclavicular or lower cervical chain node. Fine-needle aspiration has a high false-negative rate and often is inadequate to diagnose lymphoma because tissue is minimal, there is no architectural detail, and lymphomas such as Hodgkin disease may have only occasional malignant

cells in a background of normal lymphocytes. Excisional biopsy is the treatment of choice for cervical lymphadenopathy caused by atypical mycobacteria.

Summary

Palpable lymph nodes are common in children and may be a normal finding or a sign of serious disease. Because parents frequently are concerned about lymphadenopathy, the role of the primary care practitioner is to provide reassurance when appropriate and carry out a systematic evaluation when warranted. The history and physical examination frequently can elucidate the cause of the lymphadenopathy. Infectious diseases are the most common underlying cause, and antibiotics frequently are indicated if there is lymphadenitis. Generalized lymphadenopathy is less common than localized lymphadenopathy and occurs in the setting of systemic disease. Worrisome features of lymphadenopathy that should lead to additional evaluation and possible biopsy include supraclavicular location; size greater than 2 cm in a cervical lymph node; a hard, firm, or matted consistency of an enlarged lymph node; lack of associated infectious symptoms; lack of improvement over a 4-week period; and accompanying constitutional symptoms. CBC, ESR, and chest radiographs are inexpensive, useful screening tests that can aid the clinician in determining whether a biopsy should be performed.

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6. You are evaluating a 6-year-old girl who was brought to the office because of right neck swelling and redness of 2 days' duration. She has had a fever to 101°F (38.4°C) and no other recent symptoms, but her mother reports similar previous episodes several times in the past and occasional drainage from the skin in that area. Her physical examination reveals a 2×2-cm erythematous, tender mass just anterior to the right sternocleidomastoid muscle. The rest of the examination findings are normal. Which of the following is the *most* likely diagnosis?

   A. Atypical mycobacterial infection.
   B. Branchial cleft cyst.
   C. Cystic hygroma.
   D. Infectious mononucleosis.
   E. Thyroglossal duct cyst.

7. A 6-month-old boy who has no past medical history presents to the emergency department with the acute onset of left neck swelling and fever for 1 day. Physical examination reveals marked swelling of the left neck and a warm, erythematous, tender mass that measures approximately 5×4 cm in the anterior triangle. He is febrile and mildly ill-appearing. Which of the following is the *most* likely organism to cause these symptoms?

   A. An anaerobic bacterium.
   B. *Bartonella henselae.*
   C. Group B *Streptococcus.*
   D. *Mycobacterium avium* complex.
   E. *Staphylococcus aureus.*

8. A previously healthy 12-year-old girl comes to your office with the complaint of fatigue for 2 weeks, fever and sore throat for 1 week, and decreased oral intake due to throat pain. Her physical examination reveals a temperature of 101°F (38.4°C) and otherwise normal vital signs. She is tired-appearing but nontoxic. Her throat is very erythematous, with copious yellowish tonsillar discharge, and she has difficulty swallowing. Several 2×2-cm, slightly tender lymph nodes are palpable posterior to the sternocleidomastoid muscles bilaterally, and shotty inguinal lymphadenopathy is noted. Her spleen is palpable 3 cm below the costal margin. The remainder of the physical examination results are normal. Which of the following is the *most* likely diagnosis?

   A. Cat-scratch disease.
   B. Hodgkin disease.
   C. Infectious mononucleosis.
   D. Juvenile idiopathic arthritis.
   E. Kawasaki disease.

9. A 14-year-old boy is referred to the hospital for evaluation of a swollen lymph node, which his mother says has been present and growing for the past 6 weeks. The swelling has not improved after 2 weeks of amoxicillin. He has had intermittent low-grade fevers over the last 6 weeks. His physical examination reveals normal findings, with the exception of a 3×2-cm hard, nonmobile lymph node in the left supraclavicular area. Which of the following tests is *most* likely to confirm a diagnosis in this patient?

   A. Blood culture.
   B. Chest radiograph.
   C. Excisional biopsy of the node.
   D. Fine-needle aspiration of the node.
   E. Tuberculin skin test.

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