PediatricsinReview®

Lymphadenopathy

Shashi Sahai

Pediatrics in Review 2013;34;216
DOI: 10.1542/pir.34-5-216

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pedsinreview.aappublications.org/content/34/5/216

Pediatrics in Review is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1979. Pediatrics in Review is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2013 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0191-9601.

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Downloaded from http://pedsinreview.aappublications.org/ at UNIV OF CHICAGO on May 16, 2013

Lymphadenopathy

Shashi Sahai, MD*

Author Disclosure
Dr Sahai has disclosed she owns stocks/bonds in Dr. Reddy's Laboratories, Ltd., and Roche Holding, A.G. This commentary does not contain discussion of unapproved/investigative use of a commercial product/device.

Practice Gaps

1. Diffuse lymphadenopathy should always be evaluated by careful history and physical examination and perhaps laboratory investigation.
2. The absence of any palpable lymph nodes in the presence of symptoms suggesting infection in that drainage area should raise suspicion for immunodeficiency diseases.
3. Supraclavicular adenopathy is always abnormal and the chances of malignancy are high.

Objectives

After completing this article, readers should be able to:

1. Define lymphadenopathy
2. Know the differential diagnosis for localized and generalized lymphadenopathy
3. Know the etiology and evaluation of acute and chronic cervical lymphadenopathy
4. Know the age-dependent microbiology of acute cervical lymphadenitis
5. Recognize the "red flags" associated with noninfectious causes of lymphadenopathy

Introduction

Lymphadenopathy is defined as an abnormality in size and consistency of lymph nodes, while the term lymphadenitis refers to lymphadenopathy that occurs from infectious and other inflammatory processes. Lymph node enlargement is a common finding on physical examinations of children. In fact, the absence of any palpable lymph node in the presence of symptoms that suggest infection in a drainage area should raise suspicion for an immunodeficiency disease. The presence of an enlarged lymph node may be a source of anxiety in parents because of its association with malignancy. Although infections are the most common cause of lymph node enlargement, clinicians must be aware of a broad range of other disease processes that lead to lymph node enlargement.

Anatomy and Physiology

The lymphatic system is comprised of lymphatic vessels and lymphoid organs. The lymphatic vessels transport interstitial fluid back to the circulating blood. Lymph is an ultrafiltrate of blood. It is collected through the lymphatic capillaries that are present throughout the body. The brain and heart are the only organs that are devoid of lymphatic capillaries. Lymph moves with the help of the milking action of skeletal muscles and by peristalsis of lymphatic capillaries. Valves in the lymphatic vessels assure a unidirectional flow. Lymph gets into progressively larger lymphatic vessels and finally into the right lymphatic and thoracic duct.

The lymphoid organs contain lymphocytes and other cells that are responsible for the body's immunity. The bone marrow and thymus are called primary lymphoid organs because they are the sites for generation of B lymphocytes and T lymphocytes. Lymph nodes, spleen, and mucosa-associated lymphoid tissue (MALT), including tonsils, the appendix, solitary lymphoid nodules, and Peyer patches of the ileum, are the secondary lymphoid organs. Lymph nodes are present throughout the body and distributed along the path of the lymphatic vessels. They are bean shaped and encapsulated. Lymph nodes act as filters for the lymph.

The lymph enters on the convex surface of a lymph node through the afferent lymphatics. The efferent lymphatics and veins exit through the hilum. The hilum also provides an entry point for nerves and arteries. Connective tissue encapsulates the lymph node and some connective tissue enters the lymph node and forms trabeculae. The lymph courses through

*The Carman and Ann Adams Department of Pediatrics, Division of Hospital Medicine, Children's Hospital of Michigan, Wayne State University School of Medicine, Detroit, MI.

Downloaded from http://pedsinreview.aappublications.org/ at UNIV OF CHICAGO on May 16, 2013

unlined sinuses that are present along the capsule and trabeculae. During the passage of lymph from cortical to medullary sinuses, the lymph gets modified by the immune cells. Efferent lymph is rich in newly synthesized antibodies.

Histologically, a lymph node consists of a cortex, paracortex, and medulla. The most common cells in lymph nodes are lymphocytes, macrophages, plasma cells, follicular cells, and reticular cells.

Immune Responses Mediated by Lymph Nodes

There are approximately 600 lymph nodes in the body. Lymph passes through at least one lymph node in the body before getting back into the blood stream. Afferent lymph contains antigens, including partly destroyed microorganisms and antigens that are transported by antigen-presenting cells. This lymph also may contain microorganisms and cytokines from areas of inflammation and infection. Microorganisms may get phagocytosed, processed, and presented as antigens in the lymph node.

Lymphocytes proliferate in the lymph nodes. B cells mature into plasma cells and secrete antibodies. Infection and antigenic stimulation cause a lymph node to increase in size. The lymph node enlarges as a result of cellular hyperplasia, lymphocyte infiltration, and tissue edema. The swollen lymph nodes have multiple germinal centers with active cell proliferation. The symptoms associated with acute lymphadenitis reflect the pathophysiologic events that occur in response to an infection. Malignant tumor cells also reach lymph nodes and then get distributed to other parts of the body. Infiltration by malignant tumor cells also will cause a lymph node to enlarge.

Understanding the anatomy of lymph node drainage is important in identifying the site of a pathologic lesion when a lymph node is enlarged. Figures 1 and 2 illustrate the various drainage sites.

Normal Lymph Nodes

It is important to know the normal sizes of lymph nodes at different sites in healthy children. A number of studies have demonstrated enlarged and palpable lymph nodes in up to one-half of healthy neonates, infants, and older children. (1,2) Because younger children are being exposed constantly to newer antigens and inciting immune responses, lymph nodes in children usually are larger than those found in adults. Older children and adolescents have smaller lymph nodes than do younger children. Lymph nodes in the axillary and cervical regions up to 1 cm in diameter, those in the inguinal region up to 1.5 cm in diameter, and those in the epitrochlear region up to 0.5 cm in diameter are considered normal.

The evaluation of lymph node enlargement begins with a detailed history and physical examination that will assist in reaching a differential diagnosis. Further laboratory and radiologic evaluation will be decided according to the differential diagnosis developed through clinical evaluation.

History

Children usually present with the complaint of a lump in the neck, axilla, or inguinal area. The lump may be an isolated finding. However, most often it is associated with other systemic symptoms. It is important to recognize that there are other swellings (listed in Table 1), especially in the cervical area, that may be mistaken for a lymph node,

Age is important in suggesting the likely cause of lymph node enlargement. Children younger than 5 years old are more likely to have an infectious cause for their lymph node enlargement. Lymph node enlargement in neonates may represent a congenital infection such as *Toxoplasma* or cytomegalovirus (CMV). Although rare, lymphadenopathy caused by histiocytosis can occur in children younger than 3 years old. (3) The likelihood of a malignancy such as lymphoma increases in adolescents.

Location of an enlarged lymph node is important in evaluation. Cervical lymph node enlargement is a very common finding associated with viral upper respiratory infection. Supraclavicular lymphadenopathy is always abnormal and the chances of malignancy are high. In a series(3) of excisional biopsies of supraclavicular lymph nodes, the nodes were found to be abnormal in 100% of specimens and were associated with lymphoma, tuberculous or atypical mycobacterial infection, or sarcoidosis of the mediastinum. Examination of the drainage area for infectious lesions is essential. The presence of two or more noncontiguous sites of lymph node enlargement represents a generalized lymphadenopathy. Causes of generalized and localized adenopathy are outlined in Tables 2 and 3.

Time of onset and duration of lymph node enlargement should be noted. An acute enlargement is more likely to represent an acute viral or bacterial infectious process. Lymphadenopathy of longer than 4 weeks' duration is considered to be chronic. Chronic lymphadenopathy is more likely to be caused by an underlying malignant process or a chronic infection.

In order to identify a focus of infection leading to lymphadenopathy, the clinician should look for infectious lesions in the **drainage area.** The presence of sore throat, nasal congestion, red eyes with discharge, oral ulcers, dental caries, and gingival swelling should be looked for in patients who have cervical lymphadenopathy.

Downloaded from http://pedsinreview.aappublications.org/ at UNIV OF CHICAGO on May 16, 2013

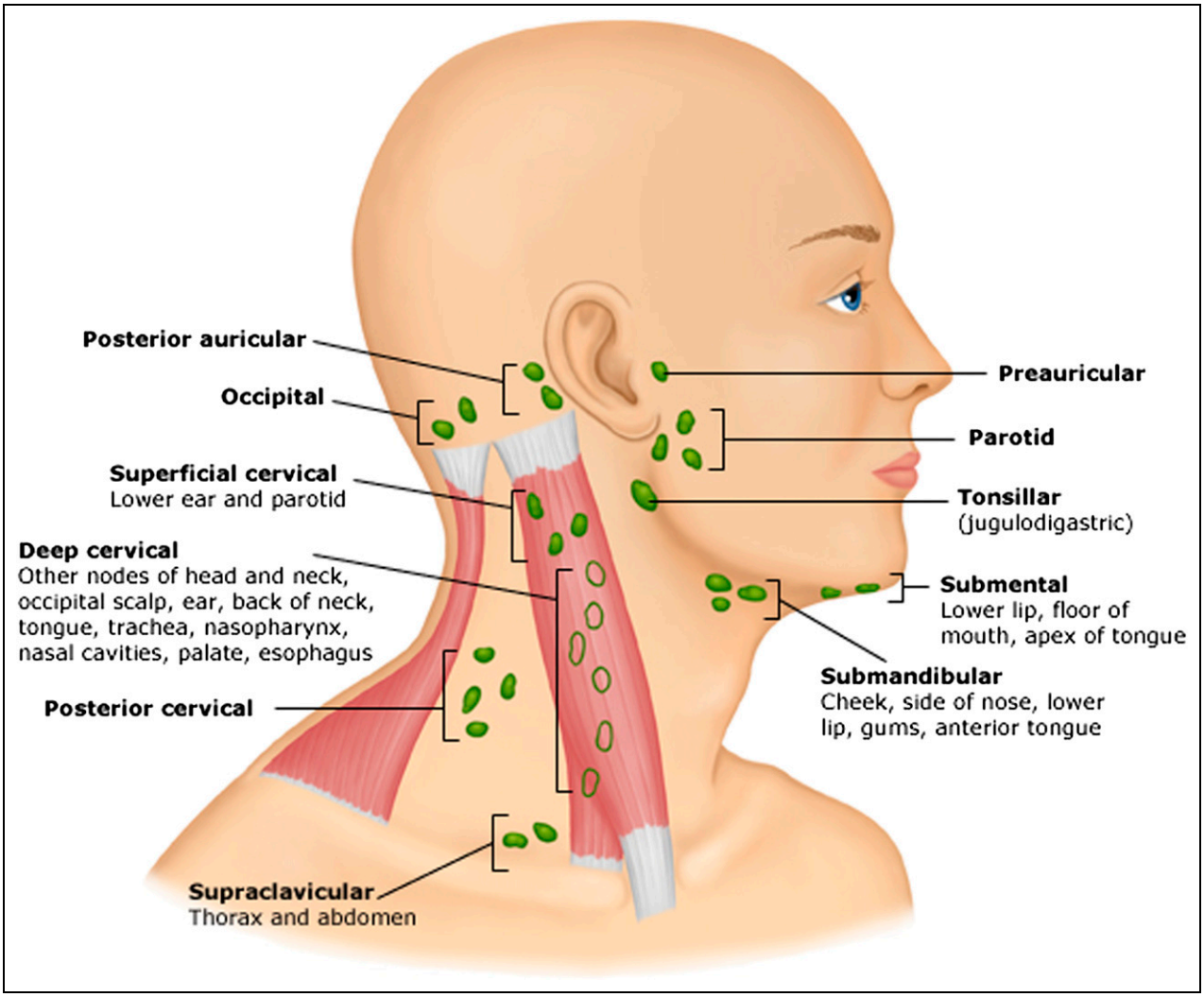

Figure 1. Lymph nodes of the head and neck and their drainage areas. Reproduced with permission from: McClain, KL, Fletcher RH. Causes of Peripheral Lymphadenopathy in Children. In: UpToDate, Basow DS (Ed), UpToDate, Waltham, MA 2013. Copyright 2013. UpToDate Inc. For more information, visit www.uptodate.com.

The presence of fevers, rash, generalized pain, joint pain and swelling, petechiae, weight loss, failure to thrive, night sweats, chronic cough, fatigue, red oral mucosa, peeling of fingers, and eczema may point to the cause of the lymphadenopathy. Symptoms of respiratory and pharyngeal compromise, such as drooling, stridor, and breathing difficulty, may mandate immediate attention. A history of recurrent infections associated with lymphadenopathy may point to a phagocyte function disorder such as chronic granulomatous disease.

Zoonoses that may present with lymphadenopathy are listed in Table 4. It is important also to obtain a history of exposure to other sick individuals. International **travel** to developing countries should be inquired about because travel may raise the possibility of diseases such as tuberculosis (TB) and leishmaniasis.

Medications such as penicillin, cephalosporins, phenytoin, and carbamazepine are known to cause generalized lymphadenopathy. Vaccine-preventable diseases such as measles, rubella, and diphtheria may present with lymphadenopathy in an unimmunized child.

Physical Examination

The presence of fever and other vital signs or pallor should be noted. Anthropometry provides important

Downloaded from http://pedsinreview.aappublications.org/ at UNIV OF CHICAGO on May 16, 2013

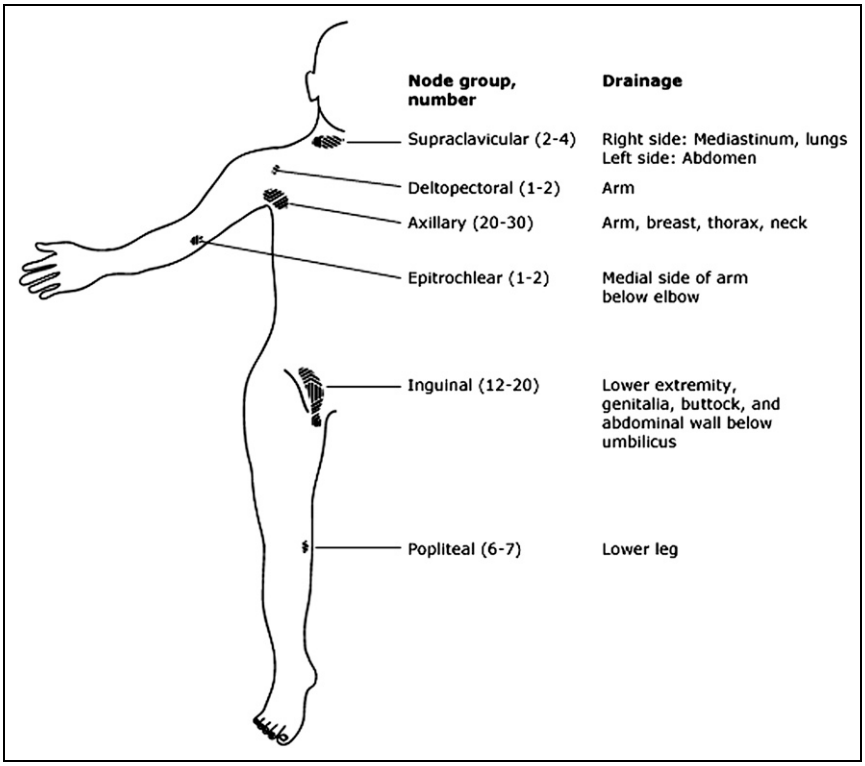

Figure 2. Lymph node regions in the body. Reproduced with permission from: McClain, KL, Fletcher RH. Causes of Peripheral Lymphadenopathy in Children. In: UpToDate, Basow DS (Ed), UpToDate, Waltham, MA 2013. Copyright 2013. UpToDate Inc. For more information, visit www.uptodate.com.

clues in cases of chronic lymphadenopathy. Poor weight gain may be present when the lymphadenopathy is caused by infections such as TB or human immunodeficiency virus (HIV) or by lymphoma.

Examination of Lymph Node and Lymphatic Organs

The size of the enlarged lymph node aids in determining the need for further evaluation. Lymph nodes larger than 2 cm are more likely to harbor a more serious disease process. The number of lymph nodes and the consistency, fluctuance, tenderness, mobility, and presence of matting should be noted. Lymphadenitis is characterized by swelling of lymph nodes in conjunction with pain, skin changes in the form of erythema and edema, and tenderness. All other areas of potential lymph node enlargement should be examined. The presence of liver and spleen enlargement should be evaluated.

It is important to examine the drainage area in cases of localized lymphadenopathy. A careful head, neck, and oropharyngeal examination may reveal a primary focus of infection. The presence of rash and petechiae may help to make the diagnosis. Conjunctival injection without exudates may be present in patients with Kawasaki disease. Exudative conjunctivitis is present in infection with *Bartonella*, adenovirus, and *Francisella tularensis* (tularemia). Bone and joint tenderness should be looked for.

Table 1. Differential Diagnosis of Lymph Node Enlargement

Lesion	Description	Location
Cystic hygroma (lymphangioma)	A compressible painless soft mass that transilluminates; may increase in size during upper respiratory infections	Supraclavicular and posterior to the sternocleidomastoid on the left side, but may extend to other areas such as the floor of the mouth and axilla
Branchial cleft cyst	Recurrent swelling that may be infected; may have a sinus or pit	Lateral neck with sinus along anterior border of the lower 2/3 of the sternocleidomastoid
Thyroglossal duct cyst	May present with infection and moves with tongue protrusion and swallowing	Midline at the level of the thyrohyoid membrane; communicates with the base of the tongue. Occasionally may be felt lateral to the midline
Cervical rib	Hard, bony feel	Supraclavicular
Thyroid nodule	Painless firm to hard	Midline in thyroid area
Sternocleidomastoid fibroma	Soft mass in the sternocleidomastoid, torticollis with chin pointing to the opposite side of hematoma	Inferior portion of sternocleidomastoid
Epidermoid cyst	Superficial, smooth	Suprasternal

Downloaded from http://pedsinreview.aappublications.org/ at UNIV OF CHICAGO on May 16, 2013

Table 2. **Differential Diagnosis of Systemic Generalized Lymphadenopathy**

Infant	Child	Adolescent
COMMON CAUSES		
Syphilis	Viral infection	Viral infection
Toxoplasmosis	EBV	EBV
CMV	CMV	CMV
HIV	HIV	HIV
	Toxoplasmosis	Toxoplasmosis
		Syphilis
RARE CAUSES		
Chagas disease (congenital)	Serum sickness	Serum sickness
Congenital leukemia	SLE, JRA	SLE, JRA
Congenital tuberculosis	Leukemia/lymphoma	Leukemia/lymphoma/Hodgkin disease
Reticuloendotheliosis	Tuberculosis	Lymphoproliferative disease
Lymphoproliferative disease	Measles	Tuberculosis
Metabolic storage disease	Sarcoidosis	Histoplasmosis
Histiocytic disorders	Fungal infection	Sarcoidosis
	Plague	Fungal infection
	Langerhans cell histiocytosis	Plague
	Chronic granulomatous disease	Drug reaction
	Sinus histiocytosis	Castleman disease
	Drug reaction	

This table was published in *Practical Strategies in Pediatric Diagnosis and Therapy*. 2nd edition, by Kliegman RM, Greenbaum LA, Lye PS, p 863. Copyright Elsevier, 2004.
Author's note: Hemophagocytic lymphohistiocytosis may also be a cause of generalized lymphadenopathy.
CMV=cytomegalovirus; EBV=Epstein-Barr virus; HIV=human immunodeficiency virus; JRA=juvenile rheumatoid arthritis (Still disease); SLE=systemic lupus erythematosus.

Investigations

After a careful history and physical examination, it is possible to narrow the differential diagnosis of lymphadenopathy. Laboratory evaluation may aid in narrowing the diagnosis of both chronic and generalized lymphadenopathy. In the presence of an acute localized lymphadenopathy, when a focus of infection has not been identified and the lymph nodes raise suspicion of a bacterial infection, a trial of antibiotics may be given before embarking on an extensive evaluation. The antibiotics chosen should provide coverage for both *Staphylococcus aureus* and group A *Streptococcus*. When *Bartonella* is suspected, it is reasonable to add azithromycin. Laboratory and imaging studies may be necessary if a lymph node does not regress after treatment or after resolution of the associated acute symptoms.

Laboratory Evaluation

COMPLETE BLOOD CELL COUNT WITH DIFFERENTIAL.

Results may show a neutrophilic leukocytosis, which can indicate an acute bacterial infection. A predominantly lymphocytic leukocytosis may be associated with Epstein-Barr virus (EBV) infection. Leukocytosis with blasts on peripheral smear is indicative of leukemia. Leukopenia with depression of the hemoglobin level and platelet count also may be indicative of bone marrow involvement with malignancy. Lymphopenia may be indicative of HIV infection or congenital immunodeficiency disorders. The erythrocyte sedimentation level (ESR) and C-reactive protein level may be used as tools to look for inflammation and infection and also might help in assessing the patient's response to treatment. Lactate dehydrogenase and uric acid levels provide a screen for rapid cell turnover associated with malignancy. High liver enzyme levels may indicate involvement of the liver due to a systemic infection or an infiltrative process.

Serology may be obtained for evidence of infection with EBV, HIV, CMV, and parvovirus. *Bartonella* serology and polymerase chain reaction studies may be needed when there is more generalized involvement. The purified protein derivative (PPD) test is a useful screen for mycobacterial infection. Interferon-gamma release assays also may be used in place of the tuberculin skin test with PPD. Specific atypical mycobacterial antigen may be used when atypical mycobacterial lymphadenitis is suspected.

Radiologic Evaluation

Chest radiograph (CXR) is an essential test in the evaluation of chronic localized and generalized lymphadenopathy and may reveal the presence of mediastinal widening due

Downloaded from http://pedsinreview.aappublications.org/ at UNIV OF CHICAGO on May 16, 2013

Table 3. Sites of Local Lymphadenopathy and Associated Diseases

- **Cervical**
  - Oropharyngeal infection (viral, group A streptococcal, staphylococcal)
  - Scalp infection
  - Mycobacterial lymphadenitis (tuberculosis and nontuberculous mycobacteria)
  - Viral infection (EBV, CMV, HHV-6)
  - Cat scratch disease
  - Toxoplasmosis
  - Kawasaki disease
  - Thyroid disease
  - Kikuchi disease
  - Sinus histiocytosis
  - Autoimmune lymphoproliferative disease
- **Anterior auricular**
  - Conjunctivitis
  - Other eye infection
  - Oculoglandular tularemia
  - Cat scratch disease
  - Facial cellulitis
  - Otitis media
  - Viral infection (especially rubella, parvovirus)
- **Supraclavicular**
  - Malignancy or infection in the mediastinum (right)
  - Metastatic malignancy from the abdomen (left)
  - Lymphoma
  - Tuberculosis
- **Epitrochlear**
  - Hand infection, arm infection*
  - Cat scratch disease
  - Lymphoma[†]
  - Sarcoid
  - Syphilis
- **Inguinal**
  - Urinary tract infection
  - Venereal disease (especially syphilis or lymphogranuloma venereum)
  - Other perineal infections
  - Lower extremity suppurative infection
  - Plague
- **Hilar (not palpable, found on chest radiograph or CT)**
  - Tuberculosis[†]
  - Histoplasmosis[†]
  - Blastomycosis[†]
  - Coccidioidomycosis[†]
  - Leukemia/lymphoma[†]
  - Hodgkin disease[†]
  - Metastatic malignancy*
  - Sarcoidosis[†]
  - Castleman disease
- **Axillary**
  - Cat scratch disease
  - Arm or chest wall infection
  - Malignancy of chest wall
  - Leukemia/lymphoma
  - Brucellosis
- **Abdominal**
  - Malignancies
  - Mesenteric adenitis (measles, tuberculosis, *Yersinia*, group A *Streptococcus*)

This table was published in *Practical strategies in pediatric diagnosis and therapy, 2nd ed*, by Kliegman RM, Greenbaum LA, Lye PS, p 864, Copyright Elsevier, 2004.
CMV=cytomegalovirus; CT=computed tomography; EBV=Epstein-Barr virus; HHV-6=human herpesvirus 6.
*Unilateral. †Bilateral.

Downloaded from http://pedsinreview.aappublications.org/ at UNIV OF CHICAGO on May 16, 2013

to lymphadenopathy from lymphoma and sarcoid. Up to two-thirds of patients who have Hodgkin lymphoma may show mediastinal widening on a CXR. Mediastinal lymph node enlargement compressing the intrathoracic airway may present with wheezing. It is important to obtain a CXR of a child who is wheezing for the first time before treating with corticosteroids. CXR also may show hilar lymph node enlargement and calcification in TB and histoplasmosis.

Radiographs of the Neck

In patients in whom airway compromise is evident, radiographs of the neck may indicate the extent of involvement and can evaluate the retropharyngeal space. A lateral neck radiograph should be obtained in inspiration, with the mouth closed and neck extended. Retropharyngeal space involvement may appear as thickening of the retropharyngeal soft tissues, with smooth, curved anterior displacement of the cervical airway and loss of the normal step-off of the posterior hypopharyngeal wall and posterior wall of the trachea.

Ultrasonography

Ultrasonography (US) is a noninvasive and nonirradiating imaging procedure that may be helpful in looking for a hypoechoic, suppurative center of a lymph node. US is more specific but less sensitive than contrast computed tomography (CT) for diagnosis of an abscess. (4) Color Doppler imaging may show the increased blood flow pattern of inflamed nodes. An experienced radiologist may be able to comment on certain specific patterns; for example, in Kawasaki disease, the lymph nodes may show a "cluster of grapes" pattern. When there is suspicion of a congenital lesion in the neck mimicking lymph nodes, ultrasonography can be a helpful technique.

Computed Tomography

When more anatomic detail is required, CT may be necessary and might be advisable before undertaking a surgical procedure. Contrast-enhanced CT is a highly sensitive modality for detecting an infection in a deep neck space but it is not very specific for identifying frank pus because the imaging findings of a phlegmon are similar to that of frank pus. CT of the neck can also be a useful test for confirming a retropharyngeal abscess.

Fine Needle Aspiration

Although fine needle aspiration might appear to be a good option for decompressing a suppurative lymph node and for obtaining a tissue specimen for histopathology, the technique has its limitations. Children will always require sedation or general anesthesia for such a procedure. Before taking the risk of sedation, it is important to recognize the limited therapeutic and diagnostic benefits of this procedure, which has a high false-negative rate and is associated with inadequate architectural detail. There is also the potential for a sinus tract formation, especially when the adenopathy is due to a mycobacterial infection.

Excisional Biopsy

An excisional biopsy will confirm the presence of malignancy or disclose the granulomatous lesions of TB or sarcoid. It is important to consider an early excisional biopsy when there is a high suspicion for malignancy. The features that make a malignancy highly likely are a supraclavicular location, hard consistency, absence of head and neck infection, rubbery consistency, fevers lasting longer than 1 week, night sweats, weight loss, mediastinal widening on chest radiograph, an abnormal blood picture suggestive of leukemia or lymphoma, and hepatosplenomegaly.

It is important for the excisional biopsy to be performed at a medical center where there is multidisciplinary support available for the diagnosis and treatment of children with cancers. Adequate staining, preparation of smears, and cultures for viruses and fungi should be performed as required. When malignancy is suspected, specimens for immunohistochemical, cytogenetic, and molecular genetic tests should be obtained. The largest accessible node should be biopsied.

The size, location, consistency, and associated clinical features must be considered in a decision to perform a lymph node biopsy. (5) See Table 5 for features that may prompt a lymph node biopsy. Fifty percent of these nodes usually turn out to be enlarged due to reactive hyperplasia. Approximately 30% are associated with a granulomatous process such as cat scratch disease, atypical mycobacterial infection, TB, or a fungal infection. Malignancy is discovered in up to 13% of the patients, and Hodgkin disease constitutes 67% of the malignancies. It is important to monitor enlarged nodes. A pathologic process may be found on a repeat biopsy even in the presence of an initial normal biopsy. In approximately one-half of all patients with chronic lymphadenopathy, a definitive diagnosis may not be established despite extensive evaluation.

Treatment

The treatment of lymphadenopathy depends on the etiology. Therapy with glucocorticoids should be avoided until a definitive diagnosis is made. Glucocorticoids will mask and delay the diagnosis of leukemia and lymphomas. Patients also may become ineligible for certain treatment protocols for leukemia and lymphoma if they have received glucocorticoids.

Downloaded from http://pedsinreview.aappublications.org/ at UNIV OF CHICAGO on May 16, 2013

Table 4. Zoonoses that Present as Lymphadenopathy

Disease	Animal/Bird	Inoculation
Cat scratch disease	Kittens	Through skin
Toxoplasmosis	Cat	Ingestion of material contaminated with cat feces
Tularemia	Multiple animals especially rodents and insects	Tick bite or skin and mucosal exposure to infected animal tissue
Brucellosis	Sheep, cattle, goat, pigs	Contact with animal fluid or consumption of unpasteurized milk products
Cutaneous anthrax	Rodents in southwestern United States	Bite of an infected flea
Histoplasmosis	Birds and bats	Inhalation exposure in heavily contaminated areas such as coops, caves, abandoned buildings
Trypanosomiasis	Antelope, goats vectored by tsetse fly in Africa	Bite by tsetse fly

Disorders Associated With Lymphadenopathy

The following is a brief description of the common disorders that present with lymphadenopathy.

Reactive Lymph Nodes

This cause of lymph node enlargement occurs as a result of reactive hyperplasia secondary to an infection in the drainage area. The reactivity occurs commonly in response to pharyngitis and upper respiratory infection. A skin infection such as impetigo or cellulitis also can cause reactive lymphadenopathy. The viruses that are associated commonly with a viral upper respiratory infection are rhinovirus, parainfluenza virus, influenza virus, respiratory syncytial virus, coronavirus, adenovirus, and reovirus. Other viral infections that may lead to generalized lymphadenopathy are CMV and EBV. Viruses that cause lymphadenopathy less frequently are mumps, measles, rubella, varicella, coxsackie, and herpes simplex viruses as well as human herpesvirus 6 (roseola).

Both the anterior and posterior groups of lymph nodes in the cervical region are involved with pharyngitis and tonsillitis. Preauricular lymph nodes are enlarged with adenoviral keratoconjunctivitis. Hepatosplenomegaly may be associated with EBV and CMV. Rashes specific for viruses such as rubella and CMV may occur in association with the lymphadenopathy. Virus-associated lymphadenopathy resolves spontaneously with resolution of the viral illness. Antiviral therapy is indicated in rare patients afflicted with immunosuppression or severe hepatitis.

Bacterial Lymphadenitis

Bacterial lymphadenitis usually results from an infectious process in the cervical area. The presentation may be acute or subacute. Table 6 lists the bacteria that can cause lymphadenitis.

ACUTE PRESENTATION OF LYMPHADENITIS. Patients who have acute lymphadenitis often experience fever, ear pain, and sore throat. Other associated findings are pharyngitis, tonsillitis, impetigo, and cellulitis in the drainage area. The infected cervical lymph node is enlarged, tender, and warm and may become fluctuant with abscess formation. It is important to recognize that retropharyngeal nodes serve as a drainage path for the nasopharynx and tonsils; hence, lymphadenitis occurs commonly in these nodes in 1- to 5-year-olds. These nodes have the potential to compromise the airway when significantly enlarged. Suppuration and perforation of retropharyngeal nodes may lead to retropharyngeal abscess formation.

Table 5. When to Consider Possible Lymph Node Biopsy

SIZE
- Greater than 2 cm
- Increasing over 2 weeks
- No decrease in size of node after 4 weeks

LOCATION
- Supraclavicular lymph node

CONSISTENCY
- Hard
- Matted
- Rubbery

ASSOCIATED FEATURES
- Abnormal chest radiograph suggestive of lymphoma
- Fever
- Weight loss
- Hepatosplenomegaly

Downloaded from http://pedsinreview.aappublications.org/ at UNIV OF CHICAGO on May 16, 2013

Table 6. **Lymphadenitis-Causing Bacteria**

Bacteria	Clinical features
ACUTE	
Streptococcus pyogenes	Associate tonsillopharyngitis
Group B *Streptococcus*	Infants, unilateral facial or submandibular swelling
Anaerobic such as *Bacteroides* species, *Peptococcus* species, *Propionibacterium* acnes, and *Fusobacterium nucleatum*	May have associated dental and gingival disease
Francisella tularensis	
Pasteurella multocida	May occur after animal bites or scratch
Yersinia pestis	Flea bites on head and neck in western United States
Haemophilus influenzae type B	
Rare gram-negative bacilli, pneumococcus, Group C streptococci, *Yersinia enterocolitica*, *Staphylococcus epidermidis*, alpha hemolytic streptococci	
SUBACUTE	
Atypical *mycobacterium* species such as *avium-intracellulare* (common), *scrofulaceum*, *kansasii* (common), *fortuitum*, *haemophilum*	Rapid onset nodal enlargement, overlying skin becomes erythematous, thin and parchment like
Mycobacterium tuberculosis	High risk groups like immigrant populations, travel or residence in endemic areas
Bartonella henselae	History of contact with kittens, large single lymph node enlargement, systemic involvement

Up to 80% of acute unilateral cervical lymphadenitis in children younger than age 5 years are due to infections with *Staphylococcus aureus* and *Streptococcus pyogenes*. Antibiotic therapy is directed at antibiotics that will cover *S pyogenes* and methicillin-resistant *S aureus*. Children older than age 5 years who have dental or periodontal disease will require coverage also for anaerobic bacteria. Patients who have high fever, poor oral intake, pain, and the potential for airway compromise from retropharyngeal involvement may require hospitalization. Identification of bacteria may be done through a culture from a primary site such as the pharynx or skin. Antibiotics are administered for 10 days or for 5 additional days after resolution of symptoms, whichever is longer. Improvement may be noted in 2 to 3 days, although complete resolution may require a few weeks.

Lymphadenitis may be complicated by an abscess formation in up to 25% of patients and surgical intervention with incision and drainage may be necessary.

SUBACUTE AND CHRONIC PRESENTATIONS.

The more common causes of subacute and chronic lymphadenopathy in children are as follows:

Atypical mycobacterial lymphadenitis. In the United States, 70% to 95% of mycobacterial lymphadenitis is due to atypical mycobacteria. Nontuberculous atypical mycobacteria are acquired from environmental source; they exist as saprophytes in water and soil. Submandibular lymphadenopathy is the most common presentation. Fifty percent of patients who have nontuberculous lymphadenitis develop an abscess. Sinus tract formation may occur in 10% of these patients. Identification of the bacteria along with a drug susceptibility profile is helpful in management. Atypical mycobacteria respond poorly to antibiotics and these infections require surgical excision. If surgery cannot be performed, a 3- to 6-month course of antibiotics is recommended. Clarithromycin or erythromycin combined with rifabutin or ethambutol may be effective.

Tuberculous lymphadenitis. The presence of 2 of the following 3 criteria has 92% sensitivity in identifying tuberculous lymphadenitis. The criteria are (1) a positive PPD skin test result, (2) an abnormal chest radiograph, and (3) contact with a person who has infectious TB. The PPD may be positive in atypical mycobacterial infection. Tuberculous lymphadenitis requires treatment with multiple antituberculous antibiotics for 18 months. Surgical treatment is required rarely.

Cat scratch disease. This infection results from entry of *Bartonella henselae* through a scratch in the skin. Exposure to a kitten and the resultant skin papule may have been forgotten by the time lymphadenopathy develops 5 days to 2 months later. Most lymphadenopathy occurs in the axillary group (50%), followed by the cervical group. Constitutional symptoms such as low-grade fever, malaise, and anorexia may be associated. This infection can be confirmed by serology. The condition resolves spontaneously in 1 to 3 months. Although the benefit of antibiotic therapy is questionable in localized disease, azithromycin is known to cause a rapid resolution of lymph node swelling. Systemic involvement can lead to hepatitis, encephalitis, endocarditis, and osteomyelitis. Antibiotics used for systemic infection with *Bartonella* are rifampin, ciprofloxacin, gentamicin, trimethoprim, sulfamethoxazole, clarithromycin, and azithromycin.

Downloaded from http://pedsinreview.aappublications.org/ at UNIV OF CHICAGO on May 16, 2013

Infectious Mononucleosis

This infection is caused by EBV, and the patient typically develops fever, malaise, sore throat, anorexia, and lymphadenopathy. Other organisms that cause mononucleosis-like illness are CMV, *Toxoplasma gondii*, adenovirus, HIV, hepatitis viruses, and rubella. EBV is transmitted by sexual contact and contact with saliva, as occurs with sharing of utensils and with kissing. The incubation period is 30 to 50 days. More than 95% of the world population is infected eventually. Most children younger than 4 years old have asymptomatic infection. Older children and adolescents have physical findings of generalized lymphadenopathy (90%), splenomegaly (50%), and hepatomegaly (10%). Patients develop marked exudative tonsillitis and petechiae over the hard palate. There may be edema of the eyelids and rash.

Some patients may present with leukocytosis, thrombocytopenia, and hemolytic anemia. The definitive diagnosis is made by serology. These patients may require a bone marrow aspiration for cytology to eliminate the possibility of a malignancy. The widely used spot test is falsely negative in patients younger than 4 years of age. The detection of immune globulin M antibody to viral capsid antigen is the most specific serologic test for diagnosis.

There is no specific treatment for infectious mononucleosis, although corticosteroids may be used for airway compromise, thrombocytopenia with bleeding, hemolytic anemia, seizures, and meningitis, but corticosteroids should be used with caution because of the danger of immunosuppression in a patient infected with oncogenic virus. Corticosteroids also may mask signs of leukemia and lymphoma temporarily. Contact sports are to be avoided for 2 to 3 weeks until the splenic enlargement resolves.

Other Infectious Agents

NOCARDIA. Infection with *Nocardia* occurs when skin gets inoculated by contact with soil and decaying vegetable matter. The content of the pustule may be cultured for diagnosis. The infection is treated with sulfonamides.

ACTINOMYCES. *Actinomyces* invades locally from the oral flora and can cause brawny induration and secondary lymph node enlargement when there is cervicofacial involvement. Diagnosis requires biopsy and histopathologic examination that shows sulfur granules. The infection is treated with a 3- to 12-month course of penicillin.

TOXOPLASMA. The intracellular protozoan *Toxoplasma gondii* is acquired via the oral route from consumption of meat or milk containing cysts and oocysts. Affected lymph nodes are discrete and tender. Patients who have severe symptoms need treatment with pyrimethamine.

HISTOPLASMA CAPSULATUM, BLASTOMYCES DERMATITIDIS, AND COCCIDIOIDES IMMITIS. These fungal agents are soil saprophytes. They are endemic to specific geographic regions in the United States. Patients have pulmonary disease and secondary nodal involvement. Diagnosis is by serology. Most infections are self-limited, but severe symptoms may require treatment.

HUMAN IMMUNODEFICIENCY VIRUS. HIV is a retrovirus transmitted by sexual contact, parenteral exposure to blood, or vertical perinatal transmission. Presentation may be in the form of fever, malaise, failure to thrive, nontender lymphadenopathy, hepatosplenomegaly, and chronic diarrhea. Diagnosis is made by serology.

Other Causes of Lymphadenopathy

Kawasaki Disease

Nontender lymphadenopathy of the anterior cervical area is an early manifestation of Kawasaki disease, an acute febrile vasculitic disorder that affects the medium-sized vessels. Other manifestations are rash, swelling of hands and feet, red oral mucosa, and nonexudative conjunctivitis. Coronary artery disease is a severe component of Kawasaki disease in up to 25% of untreated children.

Leukemia

Approximately 50% of children who have leukemia will have lymphadenopathy at presentation. Lymph nodes usually are large and grow rapidly. Other clinical manifestations are pallor, fever, petechiae, generalized pains, bruising, and hepatosplenomegaly. An associated finding is pancytopenia. The white count may be high or normal.

Lymphoma

Hodgkin disease presents as cervical or supraclavicular lymphadenopathy in the majority of patients. The lymphadenopathy usually develops over weeks and months. The nodes are nontender, discrete, firm, mobile, large, and rubbery. Approximately 30% of the children may have systemic symptoms such as fever, anorexia, weight loss, or pruritis. Non-Hodgkin lymphoma presents over a shorter duration, and patients may lack systemic symptoms. Hodgkin lymphoma is unusual in children younger than age 4 years, commonly occurring in older children and adolescents. Non-Hodgkin lymphoma is more common in children younger than age 10 years.

Other Malignancies

Neuroblastoma arising in the high thoracic and cervical sympathetic ganglia may manifest as supraclavicular lymphadenopathy and Horner syndrome. Cervical lymphadenopathy also may be a manifestation of secondary involvement

Downloaded from http://pedsinreview.aappublications.org/ at UNIV OF CHICAGO on May 16, 2013

by rhabdomyosarcoma, thyroid carcinoma, and nasopharyngeal carcinoma.

Autoimmune and Collagen Vascular Disorder

Serum sickness may present as lymphadenopathy with fever, arthritis, malaise, pruritis, and urticarial rash. Serum sickness may occur in response to a viral illness and medications such as phenytoin, penicillins, cephalosporins, and carbamazepine. Other autoimmune disorders that lead to lymphadenopathy are juvenile idiopathic arthritis, systemic lupus erythematosus, dermatomyositis, and sarcoidosis.

Autoimmune Lymphoproliferative Syndrome

Autoimmune lymphoproliferative syndrome is a genetic disorder of lymphocyte apoptosis leading to lymphadenopathy, pancytopenia, and splenomegaly. Having the condition increases the risk of developing B-cell lymphoma. Diagnosis is made according to revised diagnostic criteria from a 2009 National Institute of Health international workshop. Treatment involves the use of immunosuppressive agents.

Hemophagocytic Lymphohistiocytosis

Hemophagocytic lymphohistiocytosis is a potentially fatal hyperinflammatory disease that occurs more commonly in children younger than 4 years old. The condition presents with fever, irritability, maculopapular or petechial rash, hepatosplenomegaly, lymphadenopathy, respiratory distress, and aseptic meningitis. The diagnosis can be made in the presence of set criteria that include laboratory findings such as hypertriglyceridemia, hyperferritinemia, cytopenia, low natural killer cell activity, hemophagocytosis in bone marrow or lymph nodes, and elevated soluble CD-25 antibody levels. The condition may be associated with genetic mutation of perforin or the munc13-4 gene. The treatment and prognosis depend on the underlying cause.

Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis Syndrome

This condition is an autoinflammatory disease of unknown etiology that cycles every 2 to 9 weeks and undergoes spontaneous resolution. One manifestation is tender cervical lymphadenopathy. The condition usually presents in children who are younger than 5 years old and resolves by 10 years of age. There is no specific diagnostic test. The children experience normal health and growth between episodes. Corticosteroids and nonsteroidal anti-inflammatory drugs are used to alleviate severe symptoms. A single dose of corticosteroid is an effective agent for symptom alleviation when given at the onset of an episode. Tonsillectomy is considered a controversial therapy to treat this disease that may resolve spontaneously.

Kikuchi Disease

Kikuchi disease is known also as histiocytic necrotizing lymphadenitis. The histologic changes that occur suggest a T-cell immune response to an infectious agent. The condition presents with fever and localized cervical lymphadenopathy in an older child. Associated findings are transient rash, weight loss, night sweats, nausea, and diarrhea. The lymph nodes are firm, smooth, discrete, tender, and mobile. There may be leukopenia and an elevated ESR. Lymph node biopsy is diagnostic. There is usually spontaneous resolution of this disease.

Rosai–Dorfman Disease

Rosai-Dorfman disease is known also as sinus histiocytosis with massive lymphadenopathy. The cervical lymph nodes are large, discrete, soft, and mobile. Laboratory evaluation shows neutrophilic leukocytosis, elevation of the ESR, and hypergammaglobulinemia. A biopsy of the involved node shows hyperplasia, histiocytosis, and plasmacytosis. Progressive disease may require chemotherapy.

Summary

- **Lymphadenopathy in children results from a benign infectious process in the majority of patients; however, a wide spectrum of infectious and noninfectious conditions can cause both inflammatory and noninflammatory lymph node enlargement.**
- **It is important to recognize the signs of a malignant process in order to initiate an early evaluation.**
- **In the absence of any symptoms and signs directly suggestive of a neoplastic process, close monitoring is essential to look for resolution of an enlarged node. If the node does not regress over a period of 4 weeks, it is important to get a biopsy to exclude malignancy.**

References

1. Herzog LW. Prevalence of lymphadenopathy of the head and neck in infants and children. *Clin Pediatr (Phila).* 1983;22(7):485–487

2. Bamji M, Stone RK, Kaul A, Usmani G, Schachter FF, Wasserman E. Palpable lymph nodes in healthy newborns and infants. *Pediatrics.* 1986;78(4):573–575

3. Knight PJ, Mulne AF, Vassy LE. When is lymph node biopsy indicated in children with enlarged peripheral nodes? *Pediatrics.* 1982;69(4):391–396

4. Twist CJ, Link MP. Assessment of lymphadenopathy in children. *Pediatr Clin North Am.* 2002;49(5):1009–1025

5. Gosche JR, Vick L. Acute, subacute, and chronic cervical lymphadenitis in children. *Semin Pediatr Surg.* 2006;15(2):99–106

Suggested Reading

1. Friedman ER, John SD. Imaging of pediatric neck masses. *Radiol Clin North Am.* 2011;49(4):617–632, v

2. Nield LS, Kamat D. Lymphadenopathy in children: when and how to evaluate. *Clin Pediatr (Phila).* 2004;43(1):25–33

Downloaded from http://pedsinreview.aappublications.org/ at UNIV OF CHICAGO on May 16, 2013

PIR Quiz

This quiz is available online at http://www.pedsinreview.aappublications.org. NOTE: Learners can take *Pediatrics in Review* quizzes and claim credit online *only*. No paper answer form will be printed in the journal.

New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for *AMA PRA Category 1 Credit™*. In order to successfully complete 2013 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

In *Pediatrics in Review*, *AMA PRA Category 1 Credit™* may be claimed only if 60% or more of the questions are answered correctly. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

1. A 15-year-old boy is brought into your office for evaluation of "swollen neck glands." The patient's mother is quite concerned because her brother was diagnosed as having Hodgkin disease. You take a thorough history from the patient. Of the following components of the history, which is most suggestive of a malignant rather than an infectious cause of lymphadenopathy?
   A. Aphthous stomatitis.
   B. Chronic cough.
   C. Lymph node enlargement for less than 4 weeks.
   D. Patient younger than age 4 years.
   E. Weight loss.
2. You proceed to perform a careful physical examination of the boy. You palpate each region of the body for lymph nodes. An enlarged lymph node in which of the following locations would be most concerning for malignancy?
   A. Anterior cervical.
   B. Inguinal.
   C. Posterior cervical.
   D. Submandibular.
   E. Supraclavicular.
3. A 4-year-old girl presents with a 10-day history of unilateral anterior cervical lymph node enlargement. She has a temperature of 39.5°C. The node is approximately 2 cm in diameter, warm, and fluctuant. The only pertinent finding on physical examination is mild pharyngeal erythema. You suspect acute bacterial lymphadenitis. Of the following, which are the most likely infectious agents to cause lymphadenitis in a 5-year-old?
   A. *Bartonella* and *Staphylococcus.*
   B. Epstein-Barr virus and *Staphylococcus.*
   C. *Mycobacterium tuberculosis* and *Staphylococcus.*
   D. *Staphylococcus* and *Streptococcus.*
   E. *Toxoplasma* and *Nocardia.*
4. An 8-year-old boy presents to your clinic with progressive enlargement of a right axillary node, now tender, and daily fevers (up to 38.6°C). You discover that the boy has been playing frequently with his family's new kitten. You suspect the child may have a specific bacterial infection and he is uncomfortable enough to treat. Of the following, which is the preferred antibiotic?
   A. Amoxicillin.
   B. Azithromycin.
   C. Cephalexin.
   D. Doxycycline.
   E. Penicillin.
5. A 16-year-old girl presents with 2 weeks of fatigue, fever, and sore throat. On examination, you identify enlarged posterior and anterior cervical nodes, and a palpable spleen tip. She has mild thrombocytopenia (platelet count of 120 × $10^3/\mu L$ [120 × 10^9/L]). Of the following, which would be the most specific test to confirm the suspected diagnosis?
   A. *Bartonella henselae* antibody titers.
   B. Epstein-Barr virus antibody titers.
   C. HIV antibody titers.
   D. Throat culture for group A *Streptococcus.*
   E. White blood cell count with differential.

Downloaded from http://pedsinreview.aappublications.org/ at UNIV OF CHICAGO on May 16, 2013

Lymphadenopathy

Shashi Sahai

Pediatrics in Review 2013;34;216
DOI: 10.1542/pir.34-5-216

Updated Information & Services	including high resolution figures, can be found at: http://pedsinreview.aappublications.org/content/34/5/216
References	This article cites 7 articles, 4 of which you can access for free at: http://pedsinreview.aappublications.org/content/34/5/216#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Infectious Diseases** http://pedsinreview.aappublications.org/cgi/collection/infectious_diseases
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: /site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: /site/misc/reprints.xhtml

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Downloaded from http://pedsinreview.aappublications.org/ at UNIV OF CHICAGO on May 16, 2013