Lymphadenopathy

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It’s not a tumor.

—Arnold Schwarzenegger

Learning Objectives:
1. Define lymphadenopathy.
2. Develop a differential diagnosis for acute and chronic cervical lymphadenopathy specific to different age groups.
3. Describe key components of the history and physical exam to evaluate lymphadenopathy.
4. Discuss the diagnostic workup for pediatric patients presenting with lymphadenopathy.
5. Understand the indications for lymph node biopsy.

Primary Reference:
   http://pedsinreview.aappublications.org/content/34/5/216.full.pdf+html

CASE ONE:

You are working in the Urgent Care Clinic, and your last patient of the day is Aiden, a 5-year-old boy who presents with fever, throat pain and rhinorrhea. His father, Mr. O’Pathy states that Aiden has had the throat pain and rhinorrhea for just under a week, and he had a temperature to 100.6 yesterday. Mr. O’Pathy just thinks that Aiden has a typical cold, but he became concerned when he noticed two new, soft masses under Aiden’s chin a few days ago.

1. What is lymphadenopathy, and what are the “normal” sizes of lymph nodes in children?
Typically, clinicians think of lymphadenopathy as lymph nodes that are enlarged, but the term also includes lymph nodes that are abnormal in number or consistency. While it is difficult to exactly define a “normal” size in the pediatric population, there are general principles that should guide evaluation. The size of lymph nodes can vary with age. Lymph nodes are typically undetectable in the newborn period. In young children, lymph nodes in the cervical, axillary, and inguinal regions can become palpable as their size increases secondary to repeated antigen exposure and the development of immunity. Palpating these nodes in young children (typically younger than 5 years of age) is common. Older children and adolescents tend to have smaller lymph nodes than younger children. Axillary and cervical lymph nodes are considered to be within normal limits if up to 1 centimeter in size, in the inguinal region up to 1.5 centimeters in size, and in the epitrochlear region up to 0.5 centimeters. Any lymph node greater than 2 centimeters should be considered abnormal at any age and warrants further evaluation.

The term “shotty lymphadenopathy” is often used by clinicians to describe multiple small, mobile lymph nodes classically resembling birdshot (~2mm) or buckshot (~8mm) under the skin. This is a common, self-limited finding in children under the age of five years and is typically seen during viral illnesses. Because of the variability in size and number of nodes described as “shotty” by different authors, it may be more descriptive to record the actual size and number of the nodes (e.g., 10-12 2mm anterior cervical nodes, or 4 7-8mm left-sided inguinal nodes).

Moderators may wish to direct learners to figures 1 and 2 in the primary reference to review cervical lymph node sites and corresponding lymphatic drainage.

2. How do you broadly categorize a differential diagnosis for lymphadenopathy?
The differential diagnosis for lymphadenopathy is broad, but the most common causes can be grouped into three categories: infections, immune disorders, and malignancies. While the vast majority of lymphadenopathy is benign, self-limited, and of infectious etiology, the possibility of malignancy causes incredible angst for both parents and clinicians. Tables 2 and 3 in the Sahai article provide an extensive differential diagnosis. Haberman and Steensma offer a helpful mnemonic for etiologies of lymphadenopathy, “CHICAGO”:

C - Cancers: hematologic and solid tumor
H - Hypersensitivity syndromes: serum sickness, drug sensitivities, vaccination-related
I - Infections: viral infections, localized bacterial infections, generalized infections (brucellosis, typhoid fever), tuberculosis, and fungal infections
C - Connective tissue diseases (including systemic lupus erythematosus, rheumatoid arthritis)
A - Atypical lymphoproliferative disorders (including angioimmunoblastic lymphadenopathy)
G - Granulomatous disorders (including sarcoidosis, tuberculosis, histoplasmosis)
O - Other causes (Kikuchi disease, lipid storage diseases, amyloidosis, Kawasaki)

3. What additional information do you want to elicit on history?
Given the broad differential diagnosis of lymphadenopathy, a thorough history and physical is essential for evaluation.

In any patient presenting with lymphadenopathy, it is important to ask about systemic symptoms, including fever, weight loss, night sweats, easy bruisability, poor appetite, and fatigue. The clinician must understand the time course of the lymphadenopathy, and ask about an increase in the size or number of lymph nodes. When evaluating cervical lymphadenopathy, one should inquire about a history of upper respiratory symptoms and other signs/symptoms of head and neck infections (including otitis media, pharyngitis, and dental infections), as well as symptoms that may have resolved in the course of illness (e.g., conjunctivitis in Kawasaki disease). Travel history, as well as exposure to insects (including tick bites and mosquitoes), animals in the home (cat-scratch disease), uncooked meats (tularemia, toxoplasmosis) and unpasteurized milk (brucellosis) may also be important. In adolescents, it is appropriate to inquire about sharing drinks or kissing (EBV) and sexual history (HIV, HSV) as well. An often-missed piece of information is a patient’s medication history, as several medications may be associated with the development of lymphadenopathy including phenytoin, carbamazepine, penicillins, cephalosporins, and sulfa drugs.

As with all pediatric patients, be sure to review the patient’s immunization history. Many vaccine-preventable diseases can present with lymphadenopathy (measles, mumps, rubella). Additionally, lymphadenopathy can develop in the setting of recent vaccination due to a hypersensitivity reaction or appropriate local immune response.

CASE continued:

Mr. O’ Pathy tells you that Aiden’s fever went away with over-the-counter medicine. He noted the enlarged nodes in the last four days. He has had no weight loss, and while he has not been eating his usual foods, he has been drinking fluids without difficulty. He had one ear infection at the age of two but has otherwise had no prior head and neck infections. There are no animals in the home, no recent travel, and no known exposure to insects. He does not take any other medications.

4. What are the important physical exam findings to document in this patient with possible cervical lymphadenopathy? What characteristics of lymph nodes are most concerning for malignancy?

It is important to determine if the lymphadenopathy is localized to a single area or generalized (involvement of two or more nodal groups or sites). Localized lymphadenopathy of the anterior cervical nodes is most common in the setting of upper respiratory infections, while generalized
lymphadenopathy suggests systemic disease. Thus, the physical exam should include an evaluation of not only the cervical nodes, but also the rest of the nodal chains in the neck, as well as the axillary, epitrochlear, and inguinal nodes. An abdominal exam should also be included to check for hepatomegaly and splenomegaly.

Note the size of the nodes, whether the lymphadenopathy is unilateral versus bilateral, soft versus hard, mobile versus fixed, and tender versus non-tender. Assess the nodes for warmth, erythema, or discoloration of the overlying skin. Soft nodes that are mobile without other superficial findings are typically benign. Tender nodules are frequently associated with infection but can be seen in malignancy. Recognizing these features is essential not only to determine the etiology, but also to document a baseline to monitor for changes over time.

Lymph node location can also be helpful in determining the probability of severe disease. Lymphadenopathy in the supraclavicular region is always a red flag and raises greater concern for malignancy. The drainage patterns of lymph nodes can provide a clue, especially if the origin of the lymph shows no signs of inflammation. Enlarged posterior cervical nodes may indicate a scalp infection, while enlarged submandibular nodes are commonly seen in infections of the oral cavity. Supraclavicular nodes drain the pulmonary system as well as the GI/GU tract. Axillary nodes drain the upper extremities, breast, and thoracic wall. Inguinal nodes drain the abdomen, lower extremities, and external genitalia.

The remainder of the physical exam should be focused based on the patient’s presenting concern. In this patient, given the history of fever and throat pain, a thorough ear, nose, mouth, and throat exam would be indicated.

In summary, the clinician should always consider possible malignancy when lymph nodes are firm, matted, immobile, or persist despite antibiotic therapy. Palpable lymph nodes in the supraclavicular region are also concerning for malignancy, especially in the presence of constitutional symptoms.

CASE continued:

On exam, you note that Aiden only has enlarged nodes bilaterally in the submandibular region. The nodes vary from 0.5 cm to 1.5 cm in size, and are soft, mobile, and non-tender. You do not appreciate enlarged nodes in the supraclavicular, axillary, and inguinal areas. He does not have hepatosplenomegaly. On the remainder of the exam, you note that his oropharynx is erythematous but without exudates or gross dental abnormalities. His ear exam is notable for slight erythema in the ear canals but no bulging of the tympanic membranes. Nasal turbinates are slightly erythematous, and you see clear mucus in his nares.

5. What is your differential diagnosis and plan for this patient’s cervical lymphadenopathy? How would your differential diagnosis and management change if the lymphadenopathy were generalized?

Given the acuity of his complaints, the presence of upper respiratory symptoms, and the localized nature of the lymphadenopathy, the cervical lymphadenopathy in this patient is likely secondary to an infectious source. The differential should thus include viral upper respiratory infections, pharyngitis, or dental infections. Less likely causes to consider include cytomegalovirus, Epstein-Barr virus, cat-scratch disease, and tuberculosis.

If signs of bacterial lymphadenitis are present (e.g., warmth, tenderness) a trial of antibiotics for ten to fourteen days with monitoring for response may also be appropriate. If antibiotics are used, ensure that the medications prescribed cover for Staphylococcus aureus and Streptococcus species, as these organisms are the most common causes of bacterial lymphadenitis. One may consider broadening therapy to cover community acquired MRSA infection depending on the initial response to antibiotics. For patients with no obvious infectious symptoms, a period of watchful waiting may be considered if no other alarm features are present, though the threshold to initiate a work-up after the initial observation period should be low. Consider possible abscess formation for cases of bacterial lymphadenitis that are particularly large or persist despite two to three days of antibiotic therapy.
Ultrasonography may be helpful in these cases as a non-invasive tool to determine if an abscess is present.

In this case, as no aspects of the history or physical examination seem to suggest malignancy, an observation period of 2 to 3 weeks should be appropriate; the lymphadenopathy will likely resolve as the child’s illness improves. If the parent notes persistence of the lymphadenopathy, a return visit to initiate further work-up is indicated.

Laboratory work-up typically begins with viral serologies (including EBV, HIV, and CMV), and basic studies including a CBC with differential, ESR, and CRP. Additional testing can be ordered based on history (e.g., Bartonella henselae PCR in a patient with a history of known contact with a cat) or level of suspicion (e.g., chest radiograph to look for mediastinal lymphadenopathy if any features raise concern for malignancy).

The threshold to initiate a work-up is generally lower for generalized lymphadenopathy, and should be targeted based on concerns for the aforementioned diseases raised on history and physical. In cases of generalized lymphadenopathy, the initial work-up is similar, and may include bacterial and fungal cultures, viral serologies and monospot testing when infectious symptoms are present (remember that monospot testing is unreliable in young children and during early EBV infection, but is useful in adolescents). Test also for tuberculosis, and obtain CBC with differential, CRP, and ESR.

6. When is lymphadenopathy considered to be chronic? For a child who has a longstanding history of reported lymphadopathy or a neck mass, what other conditions should be on your differential?

Chronic lymphadenopathy is generally defined as lymphadenopathy that persists beyond six weeks. In addition to malignancy, reasons for chronic lymphadenopathy in young children include a history of repeated head and neck infections, chronic use of medications, and tropical/non-endemic diseases including tuberculosis and other mycobacterial infections, brucellosis, cat scratch disease, and tularemia. Keep in mind that there are congenital lesions that can be confused with lymphadenopathy in a pediatric patient with a neck mass. Cystic hygromas, thyroglossal duct cysts, and branchial cleft cysts should be included in your differential diagnosis.

7. When should you empirically prescribe steroids? Obtain an ultrasound? Request a biopsy?

Never prescribe steroids for a patient for lymphadenopathy until a diagnosis is made, as it can obscure or delay the diagnosis of a malignancy and can adversely affect the patient’s treatment and eligibility for clinical trials.

An ultrasound may aid in determining whether lymphadenopathy is infectious versus malignant in origin. CT or MRI may also be utilized if further definition is needed. However, imaging cannot definitively exclude malignancy (e.g., calcification can be seen in both benign and malignant conditions) so a biopsy would still need to be performed if one harbored concerns.

Biopsy should be considered at any point in the timeline if alarm features are present that raise the clinician’s concern for malignancy, including prolonged duration, location, large or increasing size, or abnormal texture.

Patients with lymph nodes that have not decreased in size in 4 to 6 weeks (especially after antibiotic therapy) or have not completely resolved in 8 to 12 weeks should be referred for biopsy. An early biopsy may also be warranted for children with nodes greater than two centimeters, and certainly for all nodes greater than three centimeters. Children with enlarged supraclavicular lymph nodes should be referred for biopsy immediately, as well as those with lymph nodes that are suggestive of malignancy (i.e., fixed, rubbery, immobile, and/or hard), particularly in the presence of constitutional symptoms (including fever for greater than one week, weight loss of more than 10% of total body weight, night sweats, and fatigue). An abnormal CBC or persistently elevated inflammatory markers are also worrisome features that should be further investigated. If a chest radiograph had revealed mediastinal adenopathy, this also would warrant biopsy of any accessible lymph node.
If these labs had not already been done, when referring for biopsy, the clinician should obtain a CBC with differential, ESR, CRP, uric acid, LDH, and ferritin. Generally, prior to biopsy, a chest radiograph should also be completed to look for a mediastinal mass.

Excisional biopsy is considered to be the gold standard though it is more invasive than fine needle aspiration (FNA). There are limitations to the use of FNA: studies have demonstrated a significant false negative rate, and the quantity of tissue obtained with an FNA may be insufficient to fully describe and classify a neoplasm. Moreover, there is a risk of sinus tract formation in the setting of a mycobacterial infection, and patients undergoing FNA may still require additional invasive interventions to reach a final diagnosis.

**Additional References:**

**Resource:**
1. Patient information on lymphadenopathy from Mayo Clinic. [http://www.mayoclinic.org/diseases-conditions/swollen-lymph-nodes/basics/definition/con-20029652](http://www.mayoclinic.org/diseases-conditions/swollen-lymph-nodes/basics/definition/con-20029652)