LYMPHADENOPATHY

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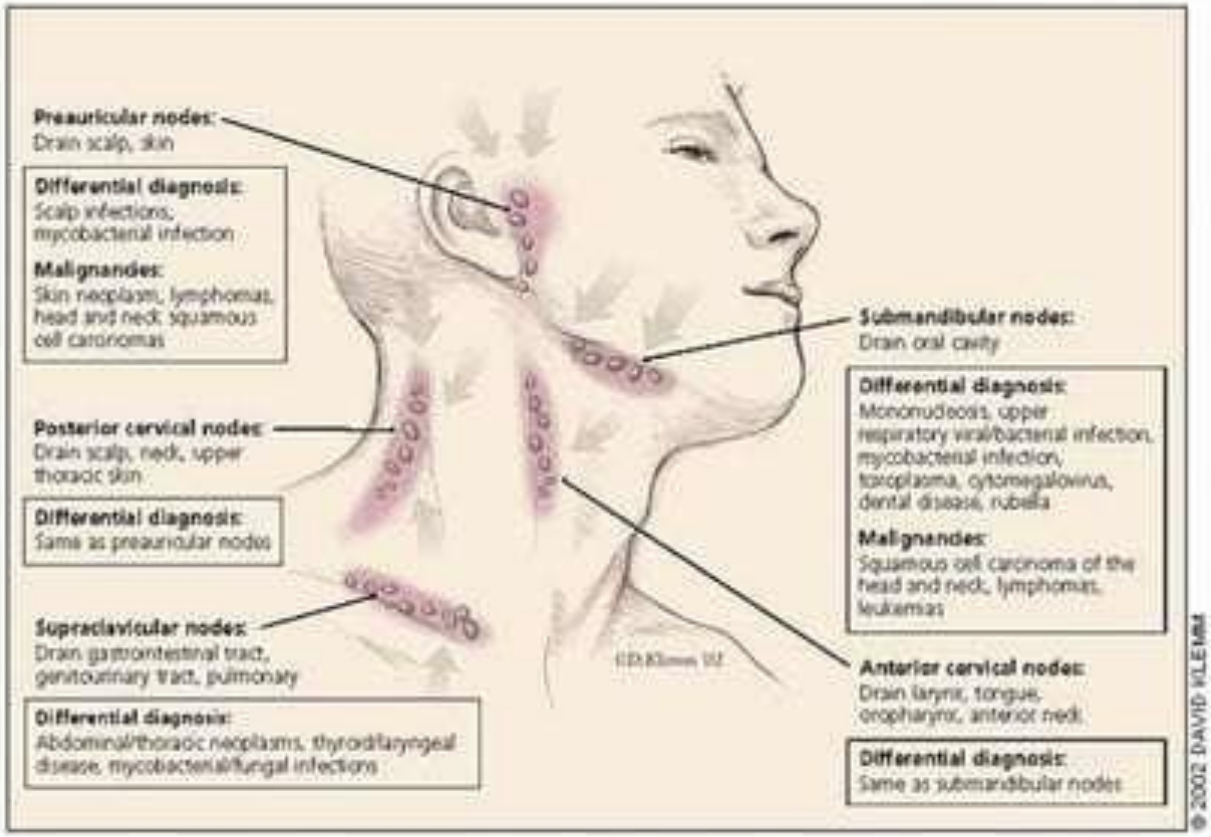
Overview

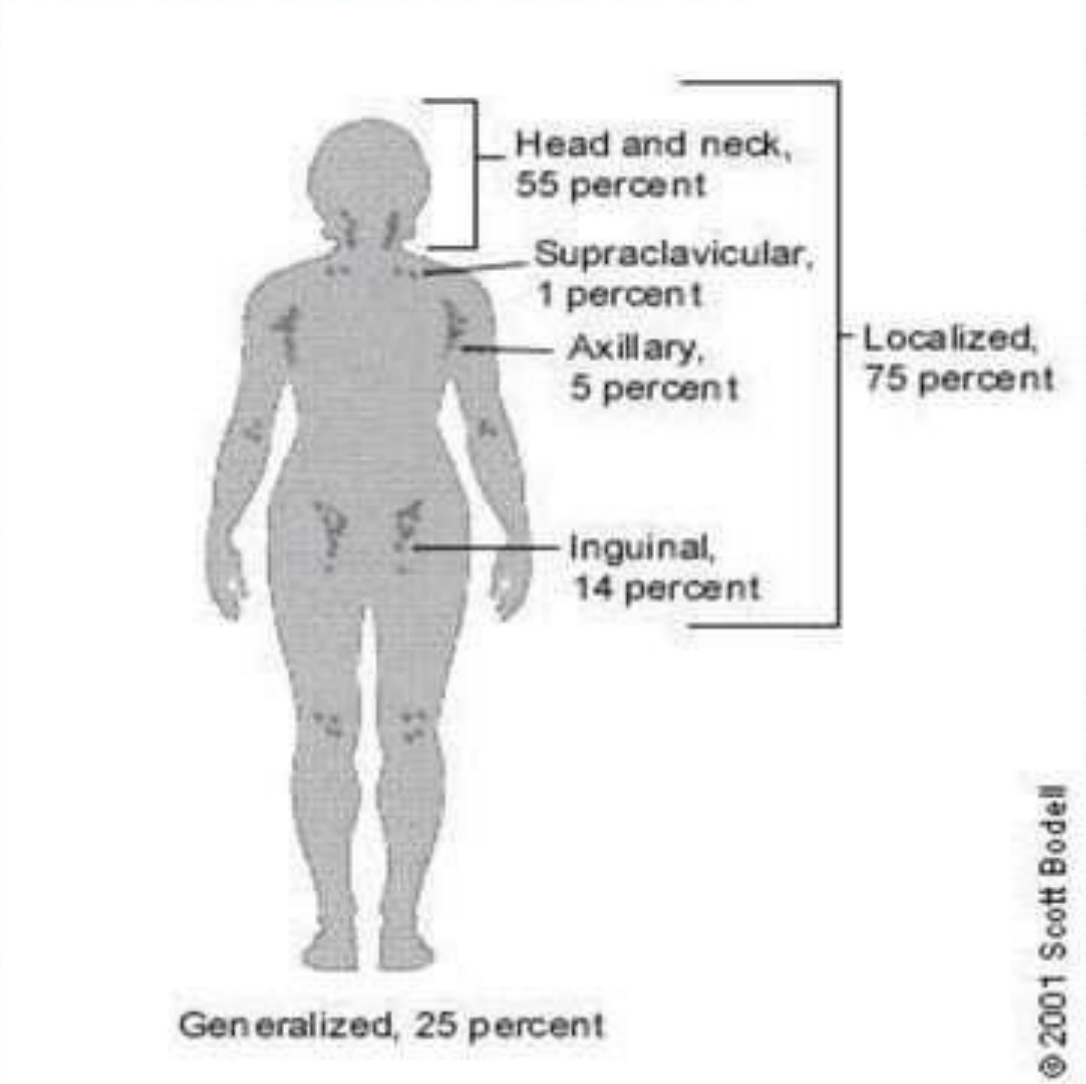
- **Lymphadenopathy** or **adenopathy** is disease of the lymph nodes, in which they are abnormal in size, number, or consistency.
- Lymphadenopathy of an inflammatory type (the most common type) is **lymphadenitis**, producing swollen or enlarged lymph nodes.
- In clinical practice, the distinction between lymphadenopathy and lymphadenitis is rarely made and the words are usually treated as synonymous. Inflammation of the lymphatic vessels is known as **lymphangitis**.

- The term comes from the word lymphand a combination of the Greek words , *adenas* ("gland") and , *patheia* ("act of suffering" or "disease").
- Lymphadenopathy is a common and nonspecific sign. Common causes include infections (from minor ones such as the common cold to dangerous ones such as HIV/AIDS), autoimmune diseases, and cancers
- Lymphadenopathy is also frequently idiopathic and self-limiting.

Lymph nodes of the head and neck, and the regions that they drain



Presentation of lymphadenopathy by anatomic site (in percentages)



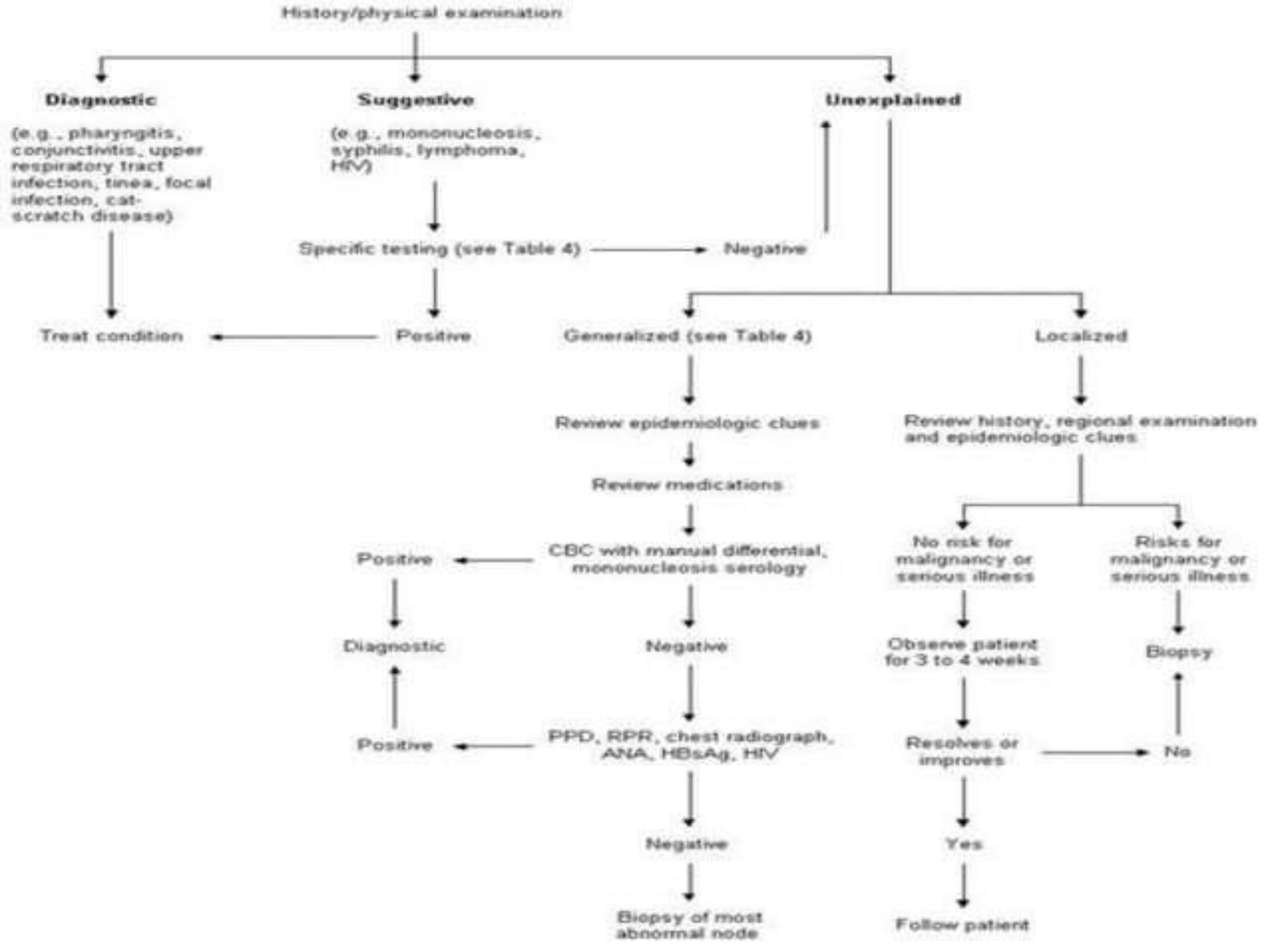
Background

- Lymph nodes, in conjunction with the spleen, tonsils, adenoids, and Peyer patches, are highly organized centers of immune cells that filter antigen from the extracellular fluid.

- The lymph node, with its high concentration of lymphocytes and antigen-presenting cells, is an ideal organ for receiving antigens that gain access through the skin or gastrointestinal tract. Nodes have considerable capacity for growth and change. Lymph node size depends on the person's age, the location of the lymph node in the body, and antecedent immunological events. In neonates, lymph nodes are barely perceptible, but a progressive increase in total lymph node mass is observed until later childhood. Lymph node atrophy begins during adolescence and continues through later life.

Diagnostic Approach to Lymphadenopathy

- A careful history and physical examination are the core of the evaluation. In most cases, a careful history and physical examination will identify a readily diagnosable cause of the lymphadenopathy, such as upper respiratory tract infection, pharyngitis, periodontal disease, conjunctivitis, lymphadenitis, tinea, insect bites, recent immunization, cat-scratch disease or dermatitis, and no further assessment is necessary.


History/physical examination
Diagnostic
(e.g., pharyngitis, conjunctivitis, upper respiratory tract infection, tinea, focal infection, cat-scratch disease)
Treat condition
Suggestive
(e.g., mononucleosis, syphilis, lymphoma, HIV)
Specific testing (see Table 4)
Negative
Positive
Unexplained
Generalized (see Table 4)
Review epidemiologic clues
Review medications
CBC with manual differential, mononucleosis serology
Positive
Diagnostic
Negative
PPD, RPR, chest radiograph, ANA, HBsAg, HIV
Positive
Negative
Biopsy of most abnormal node
Localized
Review history, regional examination and epidemiologic clues
No risk for malignancy or serious illness
Observe patient for 3 to 4 weeks
Resolves or improves
No
Yes
Follow patient
Risks for malignancy or serious illness
Biopsy

Pathophysiology

- Lymphadenopathy reflects disease involving the reticuloendothelial system, secondary to an increase in normal lymphocytes and macrophages in response to an antigen. Most lymphadenopathy in children is due to benign self-limited disease such as viral infections. Other less common etiologies responsible for adenopathy include nodal accumulation of inflammatory cells in response to an infection in the node (lymphadenitis), neoplastic lymphocytes or macrophages (lymphoma), or metabolite-laden macrophages in storage diseases (Gaucher disease).

EPIDEMIOLOGY

- Infections that are rarely observed in the United States, such as tuberculosis, typhoid fever, leishmaniasis, trypanosomiasis, schistosomiasis, filariasis, and fungal infections, are common causes of lymphadenopathy in developing nations.[3] HIV infections must be strongly considered in areas of high incidence.

Mortality/Morbidity

- In the United States, mortality and serious morbidity caused by adenopathy are unusual given the common infectious etiologies.
- Malignancies, such as leukemia, lymphomas, and neuroblastoma, are the primary causes of mortality in the United States. [4]
- Significant morbidity and mortality are also associated with autoimmune disorders (eg, juvenile rheumatoid arthritis, systemic lupus erythematosus),histiocytoses, and storage diseases.
- HIV is an uncommon cause of adenopathy in the United States, but its associated mortality requires consideration.

Causes of Generalized lymphadenopathy

- Generalized lymphadenopathy is defined as enlargement of more than 2 noncontiguous lymph node groups. A thorough history and physical examination are critical in establishing a diagnosis. Causes of generalized lymphadenopathy include infections, autoimmune diseases, malignancies, histiocytoses, storage diseases, benign hyperplasia, and drug reactions.

A)INFECTIONS

- Generalized lymphadenopathy is most often associated with systemic viral infections.
- Infectious mononucleosis results in widespread adenopathy.
- Roseola infantum (caused by human herpes virus 6), cytomegalovirus (CMV), varicella, and adenovirus all cause generalized lymphadenopathy.
- Human immunodeficiency virus (HIV) is often associated with generalized adenopathy, which may be the presenting sign. Children with HIV are at increased risk for tuberculosis, as well.[10]
- Although usually associated with localized node enlargement, some bacterial infections present with generalized adenopathy. Examples include typhoid fever caused by Salmonella typhi, syphilis, plague, and tuberculosis. Less common bacteremias, including those caused by endocarditis, result in generalized lymphadenopathies.

B)Malignant etiologies

- Concern about malignant etiologies often drives further diagnostic testing in children with adenopathy. Malignancy is often associated with constitutional signs, such as fever, anorexia, nonspecific aches and pains, weight loss, and night sweats.
- Generalized lymphadenopathy is present at diagnosis in two thirds of children with acute lymphoblastic leukemia (ALL) and in one third of children with acute myeloblastic leukemia (AML). Abnormalities of peripheral blood counts usually lead to the correct diagnosis.
- Constitutional signs and symptoms observed in the leukemias are less reliable findings in the lymphomas. Only one third of children with Hodgkin disease and 10% with non-Hodgkin lymphoma display them. Malignancies usually present with nodes that tend to be firmer and less mobile or matted; however, this finding can be misleading.

C)Storage diseases

- Generalized lymphadenopathy is an important manifestation of the lipid storage diseases. In Niemann-Pick disease, sphingomyelin and other lipids accumulate in the spleen, liver, lymph nodes, and CNS. In Gaucher disease, the accumulation of the glucosylceramide leads to the engorgement of the spleen, lymph nodes, and the bone marrow. Although widespread lymphadenopathy is common, additional findings, such as hepatosplenomegaly and developmental delay in Niemann-Pick disease and blood dyscrasias in Gaucher disease, are usually present. These diagnoses are established by leukocyte assay.

D)Drug reactions

- Adverse drug reactions can cause generalized lymphadenopathy. Within a couple of weeks of initiating phenytoin, some patients experience a syndrome of regional or generalized lymph node enlargement, followed by a severe maculopapular rash, fever, hepatosplenomegaly, jaundice, and anemia. These symptoms abate 2-3 months after discontinuation of the drug. Several other drugs are implicated in similar symptomatology, including mephenytoin, pyrimethamine, phenylbutazone, allopurinol, and isoniazid.

E)Other non-neoplastic etiologies

- Rare nonneoplastic causes of generalized lymphadenopathy include Langerhans cell histiocytosis and Epstein-Barr virus (EBV)-associated lymphoproliferative disease. Autoimmune etiologies include juvenile rheumatoid arthritis, which often presents with adenopathy, especially during the acute phases of the disease. Sarcoidosis and graft versus host disease also merit consideration.

Causes of Cervical lymphadenopathy

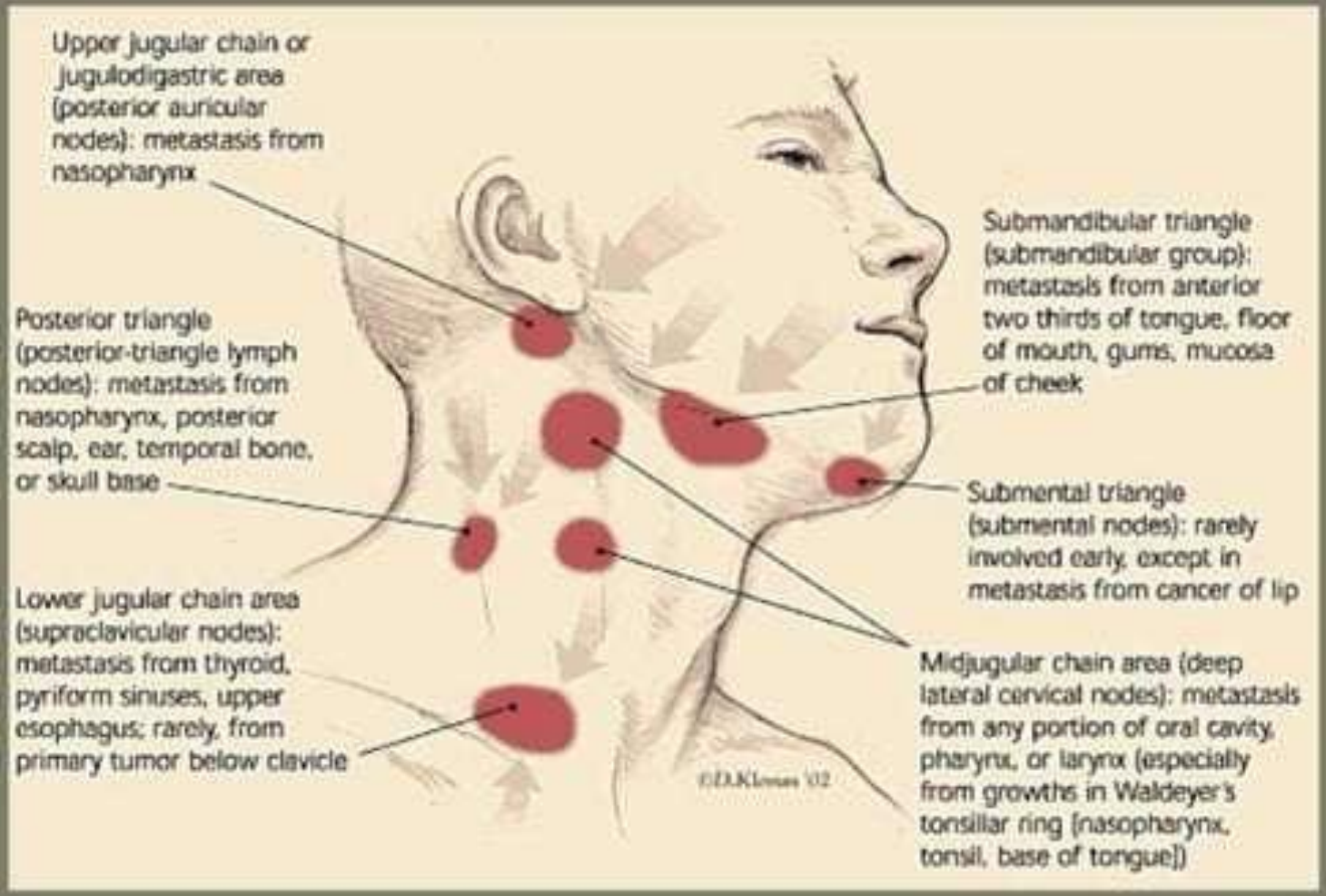
- Cervical lymphadenopathy is a common problem in children.Cervical nodes drain the tongue, external ear, parotid gland, and deeper structures of the neck, including the larynx, thyroid, and trachea.
- Inflammation or direct infection of these areas causes subsequent engorgement and hyperplasia of their respective node groups.
- Adenopathy is most common in cervical nodes in children and is usually related to infectious etiologies. Lymphadenopathy posterior to the sternocleidomastoid is typically a more ominous finding, with a higher risk of serious underlying disease.

Infectious etiologies

- Cervical adenopathy is a common feature of many viral infections.
- The classic manifestation of group A streptococcal pharyngitis is sore throat, fever, and anterior cervical lymphadenopathy.
- Atypical mycobacteria cause subacute cervical lymphadenitis, with nodes that are large and indurated but not tender. The only definitive cure is removal of the infected node.
- Mycobacterium tuberculosis may manifest with a suppurative lymph node identical to that of atypical mycobacterium..
- Catscratch disease caused by *Bartonella henselae,* presents with subacute lymphadenopathy often in the cervical region. The disease develops after the infected pet (usually a kitten) inoculates the host, usually through a scratch.

Lymphadenopathy

Cervical Lymph Nodes



Other types of LYMPHADENOPATHY

Submaxillary and submental lymphadenopathy:

- These nodes drain the teeth, tongue, gums, and buccal mucosa. Their enlargement is usually the result of localized infection, such as pharyngitis, herpetic gingivostomatitis, and dental abscess.

Occipital lymphadenopathy

- Occipital nodes drain the posterior scalp. These nodes are palpable in 5% of healthy children. Common etiologies of occipital lymphadenopathy include tinea capitis, seborrheic dermatitis, insect bites, orbital cellulitis, and pediculosis. Viral etiologies include rubella and roseola infantum. Rarely, occipital lymphadenopathy may be noted after enucleation of the eye for retinoblastoma.

Preauricular lymphadenopathy:

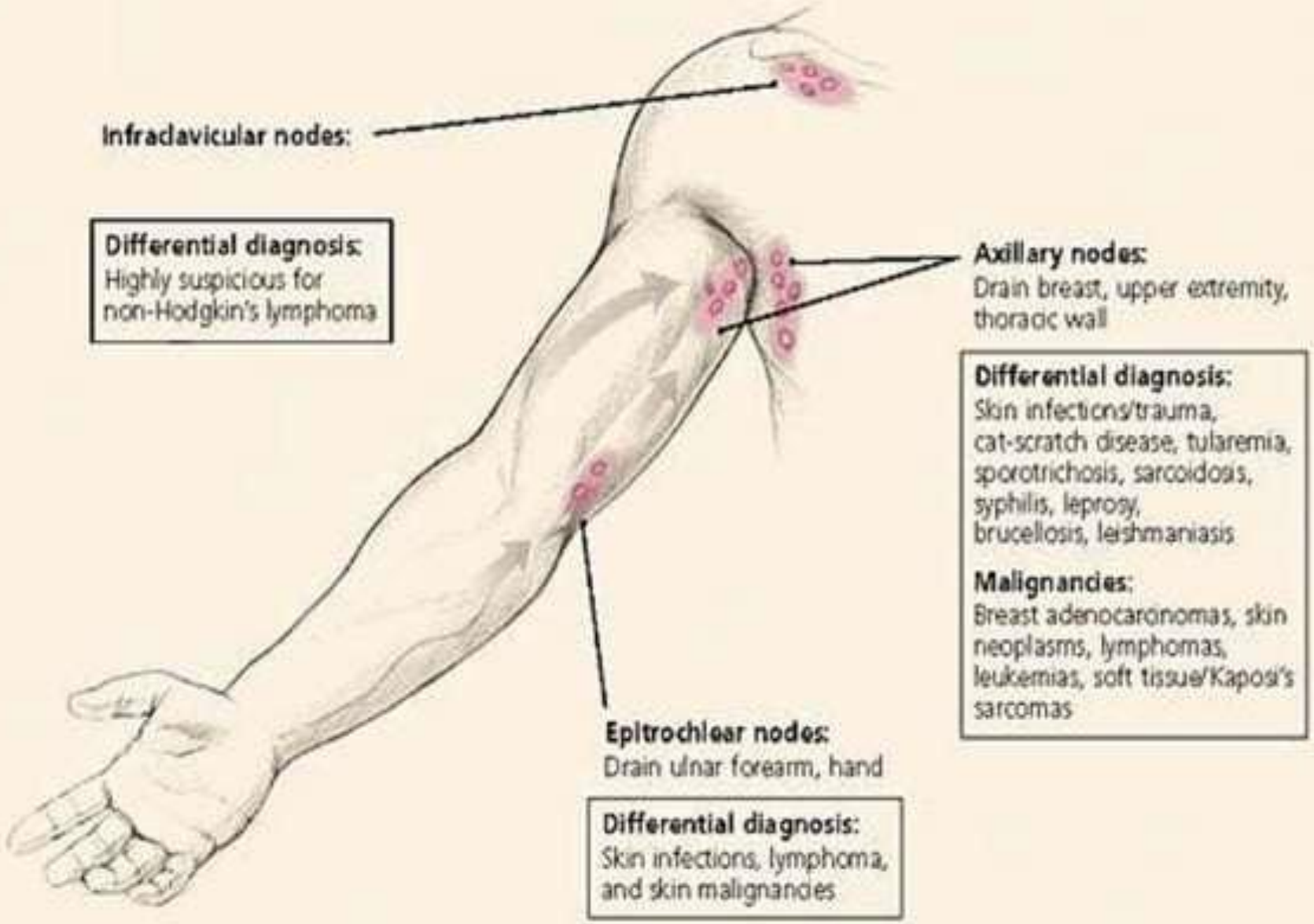
- Preauricular nodes drain the conjunctivae, skin of the cheek, eyelids, and temporal region of the scalp and rarely are palpable in healthy children. The oculoglandular syndrome consists of severe conjunctivitis, corneal ulceration, eyelid edema, and ipsilateral preauricular lymphadenopathy. Chlamydia trachomatis and adenovirus can cause this syndrome.

Supraclavicular lymphadenopathy

- Supraclavicular nodes drain the head, neck, arms, superficial thorax, lungs, mediastinum, and abdomen. Left supraclavicular nodes also reflect intra-abdominal drainage and enlarge in response to malignancies in that region. This is particularly true when adenopathy in this region occurs in the absence of other cervical adenopathy.

Axillary lymphadenopathy

- Axillary nodes drain the hand, arm, lateral chest, abdominal walls, and the lateral portion of the breast.
- A common cause of axillary lymphadenopathy is catscratch disease. Local axillary skin infection and irritation commonly are associated with local adenopathy. Other etiologies include recent immunizations in the arm (particularly with bacille Calmette-Guerin vaccine), brucellosis, juvenile rheumatoid arthritis, and non-Hodgkin lymphoma

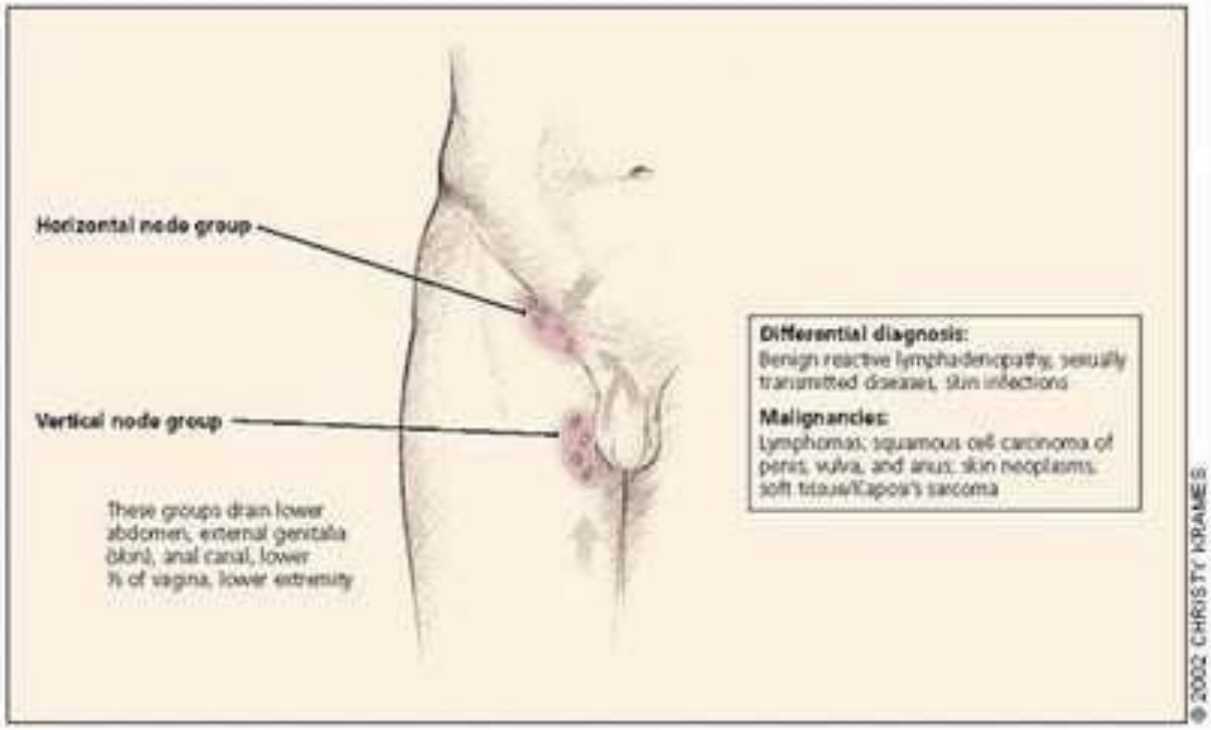


Abdominal lymphadenopathy

- Abdominal nodes drain the lower extremities, pelvis, and abdominal organs. Although abdominal adenopathy is not usually demonstrable upon physical examination, abdominal pain, backache, increased urinary frequency, constipation, and intestinal obstruction secondary to intussusception are possible presentations

Iliac and inguinal lymphadenopathy

- The lower extremities, perineum, buttocks, genitalia, and lower abdominal wall drain to these nodes. They are typically palpable in healthy children, although they are usually no larger than 1-1.5 cm in diameter. Regional lymphadenopathy is typically caused by infection; however, insect bites and diaper dermatitis are also frequent. Nonlymphoid masses that may be confused with adenopathy include hernias, ectopic testes, and lipomas.


Horizontal node group
Vertical node group
These groups drain lower abdomen, external genitalia (skin), anal canal, lower ⅓ of vagina, lower extremity
Differential diagnosis:
Benign reactive lymphadenopathy, sexually transmitted diseases, skin infections
Malignancies:
Lymphomas; squamous cell carcinoma of penis, vulva, and anus; skin neoplasms; soft tissue/Kaposi's sarcoma
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CLINICAL PRESENTATION

HISTORY

- The differential diagnosis of acute lymphadenopathy is broad. A patient's medical history and review of systems is important in narrowing this differential. Upon examination, recognizing the pattern of lymph drainage aids in seeking an infectious focus.
- Although the underlying etiology is often self-limited infection, more serious underlying etiologies must be quickly recognized.
- In adolescents, screening for intravenous drug use and sexual activity is important.

PHYSICAL EXAMINATION

- When lymphadenopathy is localized, the clinician should examine the region drained by the nodes for evidence of infection, skin lesions or tumors
- Other nodal sites should also be carefully examined to exclude the possibility of generalized rather than localized lymphadenopathy.
- Careful palpation of the submandibular, anterior and posterior cervical, supraclavicular, axillary and inguinal nodes can be accomplished in a short time and will identify patients with generalized lymphadenopathy

- If lymph nodes are detected, the following five characteristics should be noted and described:
  1. Size
  2. Pain/Tenderness
  3. Consistency
  4. Matting
  5. Location
  6. Mobility
  7. Tissue Invasion

1.SIZE

- Nodes are generally considered to be normal if they are up to 1 cm in diameter; however, some authors suggest that epitrochlear nodes larger than 0.5 cm or inguinal nodes larger than 1.5 cm should be considered abnormal.
- Little information exists to suggest that a specific diagnosis can be based on node size. However, in one series of 213 adults with unexplained lymphadenopathy, no patient with a lymph node smaller than 1 cm^2 (1 cm × 1 cm) had cancer, while cancer was present in 8 percent of those with nodes from 1 cm^2 to 2.25 cm^2 (1 cm × 1 cm to 1.5 cm × 1.5 cm) in size, and in 38 percent of those with nodes larger than 2.25 cm^2 (1.5 cm × 1.5 cm).
- In children, lymph nodes larger than 2 cm in diameter (along with an abnormal chest radiograph and the absence of ear, nose and throat symptoms) were predictive of granulomatous diseases (i.e., tuberculosis, cat-scratch disease or sarcoidosis) or cancer (predominantly lymphomas). These studies were performed in referral centers, and conclusions may not apply in primary care settings.

2.PAIN/TENDERNESS

- When a lymph node rapidly increases in size, its capsule stretches and causes pain. Pain is usually the result of an inflammatory process or suppuration, but pain may also result from hemorrhage into the necrotic center of a malignant node. The presence or absence of tenderness does not reliably differentiate benign from malignant nodes

3.CONSISTENCY

- Stony-hard nodes are typically a sign of cancer, usually metastatic. Very firm, rubbery nodes suggest lymphoma. Softer nodes are the result of infections or inflammatory conditions. Suppurant nodes may be fluctuant. The term “shotty” refers to small nodes that feel like buckshot under the skin, as found in the cervical nodes of children with viral illnesses.

4.MATTING

- A group of nodes that feels connected and seems to move as a unit is said to be “matted.” Nodes that are matted can be either benign (e.g., tuberculosis, sarcoidosis or lymphogranuloma venereum) or malignant (e.g., metastatic carcinoma or lymphomas)

5.LOCATION

- The anatomic location of localized adenopathy will sometimes be helpful in narrowing the differential diagnosis. For example, cat-scratch disease typically causes cervical or axillary adenopathy, infectious mononucleosis causes cervical adenopathy and a number of sexually transmitted diseases are associated with inguinal adenopathy.

6.Mobility

- Fixed or matted nodes suggest metastatic carcinoma, whereas freely movable nodes may occur in infections, collagen vascular disease and lymphoma. Evaluation of the mobility of supraclavicular nodes is enhanced by having the patient perform a Valsalva manoeuvre

7.Tissue Invasion

- Lymphovascular invasion (LVI or lymphovascular space invasion) is spread of a cancer to the blood vessels and/or lymphatics.
- Has got prognostic significance in some cancers

Prognostic significance in...

- ■Breast cancer
- LVI is not an independent risk factor for a poorer prognosis.
- ■Urothelial carcinoma
- LVI is an independent predictor of a poorer prognosis that has more predictive power than tumour stage.
- ■Colorectal cancer
- LVI of a poorer prognosis.

TREATMENT & MANAGEMENT

Medical Care

- Treatment is determined by the specific underlying etiology of lymphadenopathy.
- Most clinicians treat children with cervical lymphadenopathy conservatively. Antibiotics should be given only if a bacterial infection is suspected. This treatment is often given before biopsy or aspiration is performed.
- However, the risks of surgery often outweigh the potential benefits of a brief course of antibiotics. Most enlarged lymph nodes are caused by an infectious process. If aspects of the clinical picture suggest malignancy, such as persistent fevers or weight loss, biopsy should be pursued sooner.
- Management of superior vena cava syndrome requires emergency care, including chemotherapy and possibly radiation therapy.

Surgical care

- Surgical care usually involves a biopsy. If lymphadenitis is present, aspirate may be needed for culture, and removal of the affected node may be indicated.

Medical therapy

- No specific medical therapy for lymphadenopathy is acknowledged.
- Therapy is directed at the specific diagnosis, once established, and when appropriate.

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thank
you!