INTRODUCTION

The lymphatic system is an important component of the immune system. It includes lymphatic fluid, lymphatic vessels, lymph nodes, spleen, tonsils, adenoids, Peyer patches, and the thymus. Lymphatic fluid consists of an ultrafiltrate of blood collected within lymphatic channels, which run throughout the entire body. The fluid is slow-moving and is transported from the head and extremities to larger vessels, which then drain into the venous system. Along these channels reside approximately 600 lymph nodes.[1]

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. Directly interior to the fibrous capsule is the subcapsular sinus. This allows lymph, an ultrafiltrate of blood, to traverse from the afferent lymph vessels, through the sinuses, and out the efferent vessels. The sinuses are studded with macrophages, which remove 99% of all delivered antigens.[2]

Lymph nodes are composed of follicles and contain an abundance of lymphocytes. Lymph is filtered through the lymph node sinuses, where particulates and infectious organisms are detected and removed. Because of the exposure to immune challenges, antibody and cell-mediated immunity is mediated. As a result of such normal processes, the lymph nodes can enlarge by proliferation of normal cells or infiltration by abnormal cells.[3]

Interior to the subcapsular sinus is the cortex, which contains primary follicles, secondary follicles, and the interfollicular zone. Follicles within the cortex are major sites of B-cell proliferation, whereas the interfollicular zone is the site of antigen-dependent T-cell differentiation and proliferation. The deepest structure within the lymph node is the medulla, consisting of cords of plasma cells and small B lymphocytes that facilitate immunoglobulin secretion into the exiting lymph.[4]

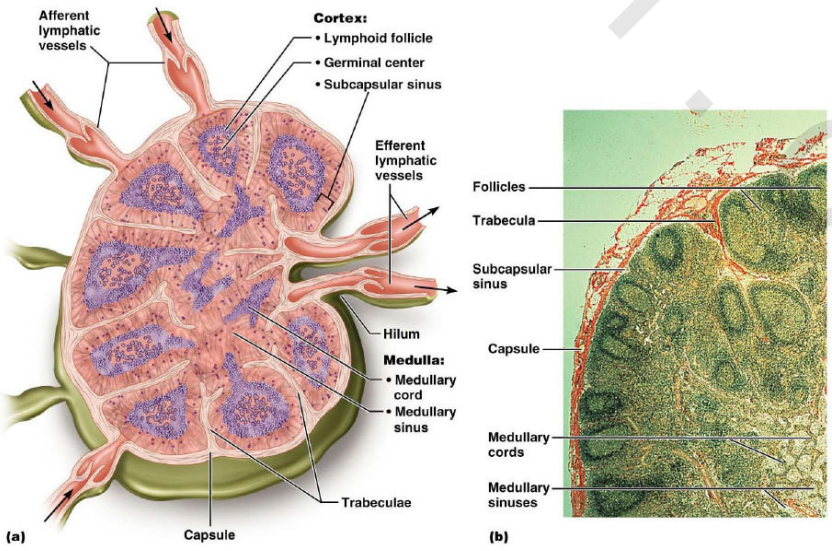

Figure (1): Structure of a Lymph Node [5,6]

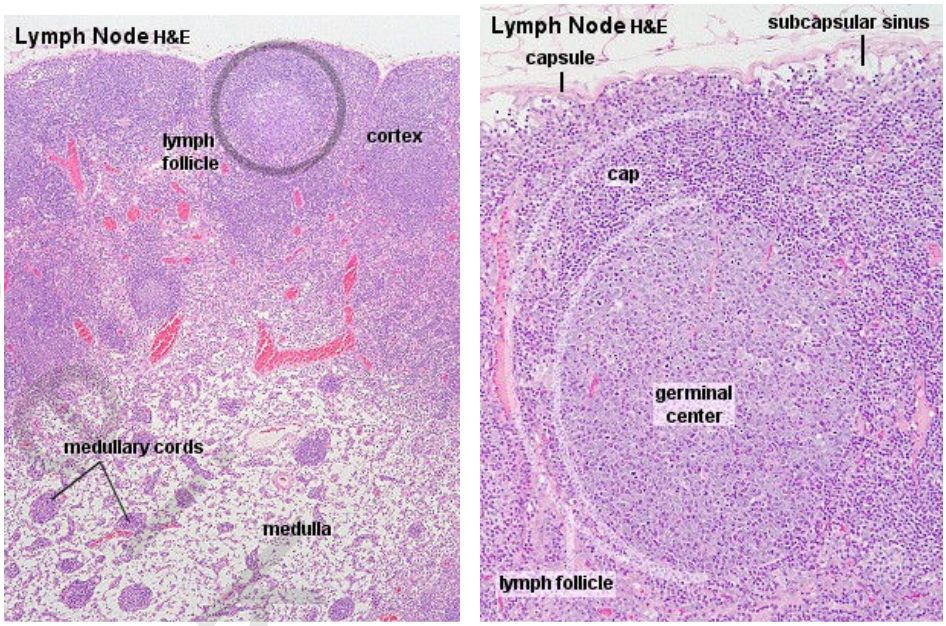

Figure (2): Lymph node, human- H&E .[7,8]

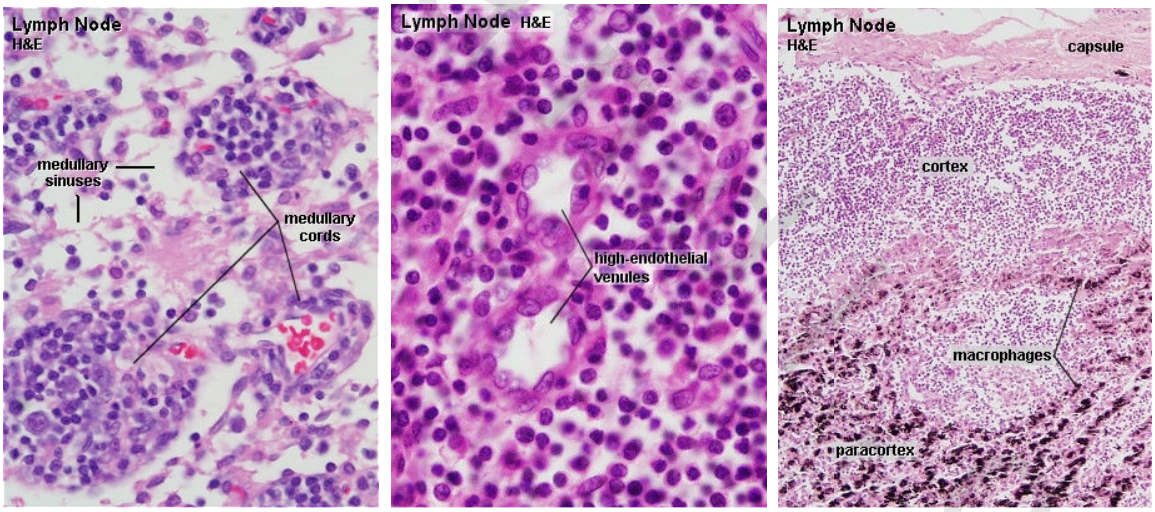

Figure (3): Lymph node - H&E, carbon injected: This slide illustrates the distribution of macrophages in lymph nodes .[7,8]

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.[9,10]

An initial insult such as an upper respiratory infection, pharyngitis, odontogenic infection or otitis media starts in the head and neck region. After a local inflammatory reaction occurs, organisms from the initial site are carried to the draining lymph nodes via afferent lymphatics. Once in the lymph nodes dendritic cells and macrophages trap, phagocytose, degrade, and present the organisms as antigens on MHC molecules. These antigens are presented to T cells for which leads to proliferation of clonal cells and release of cytokines important for chemotaxis of other inflammatory cells. One such cell is the B cell. B cells, with the help of T cells are activated, proliferate, and release immunoglobulins that aid in the immune response. The result of this immune response within the lymph node is cellular hyperplasia, leukocyte infiltration, tissue edema, vasodilation and capillary leak, and capsule distension leading to tenderness.[11, 12]

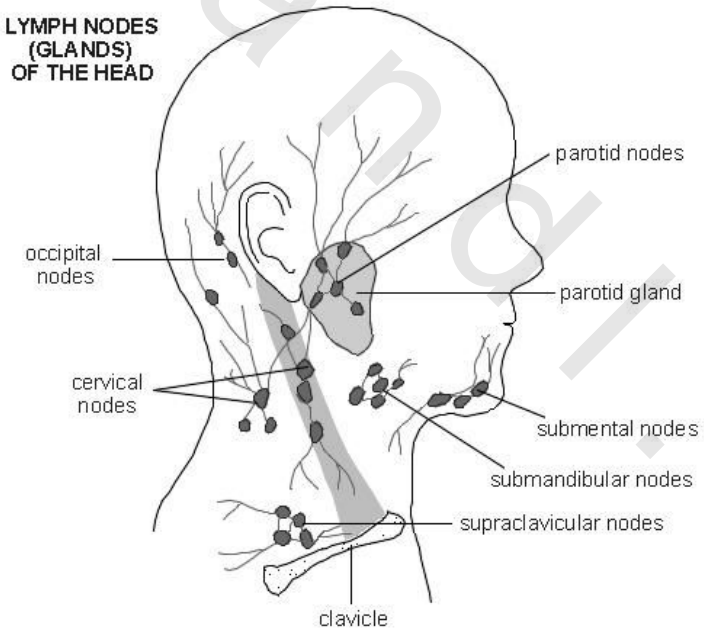

Figure (4): Lymph nodes (glands) of the head[13]

The lymph nodes enlarge due to proliferation of the lymphocytes in the lymph nodes in response to infection or due to lymphoproliferative disorder, and also due to infiltration of lymph nodes by inflammatory or malignant cells. Infection is the most common trigger for lymph node enlargement in children.[14]

A pathologic or abnormal lymph node is commonly quoted to be >1cm in size. Acute lymphadenopathy is 2 weeks duration, subacute is 2-6 weeks duration, and chronic is considered any lymphadenopathy that does not resolve by 6 weeks.[15]

Acute Lymphadenopathy:

Acute lymphadenopathy is almost always due to infectious causes and again lasts less than 2 weeks duration. Viral lymphadenopathy is the most common form of reactive lymphadenopathy. Common viruses implicated in the formation of lymphadenopathy are Adenovirus, Rhinovirus, Enterovirus' such as Coxsackie A and B, and Epstein Barr Virus. Lymphadenopathy is often diffuse, bilateral, and nontender. Patients will commonly complain of cough, rhinorrhea, and low grade fever. Management is usually expectant however because lymph nodes often persist longer than 2 weeks they are commonly biopsied. Secondary bacterial infection does occur at times in these patients.[16, 17]

Subacute Lymphadenopathy:

Subacute lymphadenopathy persists for 2-6 weeks and again is most commonly infectious in nature. These patients are typically treated with antibiotics first, however when they don't get better, therefore more aggressive workup is necessary. [16, 17]

Chronic Lymphadenopathy:

Once a lymph node has been present for greater than 6 weeks, the risk of malignancy increases especially if the mass is enlarging or the patient is experiencing systemic signs and symptoms. Subacute pathogens, however, are still implicated as it can take months for subacute disease, once diagnosed, to resolve without surgical therapy. Because malignancy is more common in this group than any other it is important to know the demographics of the patients you are taking care of. In children, there are very few common malignancies found to cause lymphadenopathy. Leukemia and lymphoma are by far the most common. Aside from these two entities, Neuroblastoma and nodal metastases are the next most common malignancies. Supraclavicular and posterior triangle lymphadenopathy are all much more suspicious for malignancy.[17]

Almost all of these patients in this group will require most often a fine needle aspiration. Excisional biopsy is often needed, because FNA does not always provide enough tissue for diagnosis if a malignancy is present.[11,14-16]

Pediatric cervical lymphadenopathy is a challenging medical condition for the patient, the parent, and the physician because thirty eight to forty five percent of normal healthy children and 90% of children aged 4-8 years old will have cervical lymphadenopathy. Although the majority of these masses will be benign the fear of malignancy is ever present.[18]

The challenge is to satisfy the parents' fears of malignancy and to do so in a safe, timely, and cost-effective manner. Organizing the possible causes of lymphadenopathy by anatomic location and origin aids the clinician in the evaluation. A rational approach is provided to determine the etiology of the lymph node disorder, and various disorders are

highlighted to consider when treating a child with lymphadenopathy. Furthermore, various means are discussed for obtaining a tissue diagnosis when the cause of lymphadenopathy is uncertain.[19, 20]

The most difficult task for the primary care physician occurs when the initial history and physical examination are not suggestive of a diagnosis that can be pursued with specific testing. Use of a short course of antibiotics or corticosteroids in the patient with unexplained lymphadenopathy is common. However, there is no evidence to support this practice, which should be avoided because it may hinder or delay diagnosis. The patient's level of concern should be addressed early and often, with provocative questioning, if necessary.[20]

I. History

1. Exposures:

A complete exposure history is essential to determine the etiology of lymphadenopathy. Exposure to animals and biting insects, chronic use of medications, infectious contacts, and a history of recurrent infections are essential in the evaluation of persistent lymphadenopathy. Travel-related exposures and immunization status should be noted, because many tropical or non-endemic diseases may be associated with persistent lymphadenopathy, including tuberculosis, trypanosomiasis, scrub typhus, leishmaniasis, brucellosis, plague, and anthrax.[21]

Environmental exposures such as tobacco and ultraviolet radiation may raise suspicion for metastatic carcinoma of the internal organs, cancers of the head and neck, and skin malignancies, respectively. Patients with acquired immunodeficiency syndrome (AIDS) have a broad differential of causes of lymphadenopathy, and rates of malignancies such as non-Hodgkin's lymphoma and Kaposi's sarcoma are increased in this group. Family history may raise suspicion for certain neoplastic causes of lymphadenopathy .[22]

Information regarding family and social history is helpful to exclude associated malignancies and is useful to allay fears that cancer can run in the family. Social history may elicit potential sources of lymphadenopathy, including drinking of unsanitized water, exposure to animals that may carry unique infections, exposure to tuberculosis (TB), exposure to typhoid, and exposure to trypanosomiasis. If the history is otherwise unremarkable, a thorough review of symptoms may establish other aspects of cause.[23]

There are very few medications that can cause lymphadenopathy but knowing about them can help one find a benign cause for a relatively worrisome lymphadenopathy. Phenytoin is classically the most common medication causing lymphadenopathy. Any child with a seizure disorder that has been on it for some time may be at risk. Other medications implicated are isoniazide, phenylbutazone, allopurinol, pyrimethamine. Lymphadenopathy usually resolves once the medication has been discontinued but long term phenytoin use has reports of prolonged adenopathy. [24]

Immunizations can also cause adenopathy. Historically the small pox vaccine was one of the most common but now in children MMR, DPT, and polio vaccines are the most commonly implicated. Typhoid fever vaccine can also be a cause, but adenopathy usually resolves with time.[24]

Table (1): Generalized lymphadenopathy cause in paediatric.[25]

Infectious
- Viral (most common): URTI, measles, varicella, rubella, hepatitis, HIV, EBV, CMV, adenovirus
- Bacterial: syphilis, brucellosis, tuberculosis, typhoid fever, septicemia
- Fungal: histoplasmosis, coccidioidomycosis
- Protozoal: toxoplasmosis

Non-infectious inflammatory diseases
- Rheumatologic diseases: Sarcoidosis, rheumatoid arthritis, SLE
- Storage diseases: Neimenn-Pick disease, Gaucher disease
- Serum sickness
- Rosai-Dorfman disease

Malignant: leukemia, lymphoma, neuroblastoma
Drug reaction: phenytoin, allopurinol
Hyperthyroidism

Localized
enlargement of a single node or multiple contiguous nodal regions

A. **Cervical** (most common adenopathy in children, often infectious cause):
Infectious:
1. Viral upper respiratory infection
2. Infectious mononucleosis (EBV, CMV)
3. Group A Streptococcal pharyngitis
4. Acute bacterial lymphadenitis (e.g staphylococcus aureus)
5. Kawasaki disease (unilateral cervical lymph node > 1.5 cm)
6. Rubella
7. Catscratch disease
8. Toxoplasmosis
9. Tuberculosis, atypical mycobacteria

Neoplastic: (malignant childhood tumours develop in the head and neck in ¼ of cases. Neuroblastoma, leukemia, non-Hodgkins, and rhabdomyosarcoma are most common in those < 6 years old. In older children, Hodgkin's and non-Hodgkin's lymphoma are more common.
1. Acute leukemia
2. Lymphoma
3. Neuroblastoma
4. Rhabdomyosarcoma

B. **Submaxillary and submental**
1. Oral and dental infections
2. Acute lymphadenitis

C. **Occipital**
1. Pediculosis capitis (lice)
2. Tinea capitis/local skin infection
3. Rubella
4. Roseola

D. **Preauricular** (rarely palpable in children)
1. Local skin infection
2. Chronic ophthalmic infection

E. **Mediastinal** (not directly palpable; assess indirectly via presence of supraclavicular adenopathy. May manifest as cough, dysphagia, hemoptysis, or SVC syndrome – this is a medical emergency!)
1. ALL
2. Lymphoma
3. Sarcoidosis
4. Cystic fibrosis
5. Granulomatous disease (tuberculosis, histoplasmosis, coccidioidomycosis)

Table (1): Cont.

F. **Supraclavicular** (associated with serious underlying disease) 1. Lymphoma 2. Tuberculosis 3. Histoplasmosis 4. Coccidioidomycosis G. **Axillary** 1. Local infection 2. Cat scratch disease 3. Brucellosis 4. Reactions to immunizations 5. Non Hodgkin lymphoma 6. Juvenile rheumatoid arthritis 7. Hidradenitis suppurativa H. **Abdominal** (may manifest as abdominal pain, backache, urinary frequency, constipation, or intestinal obstruction due to intussuception) 1. Acute mesenteric adenitis 2. Lymphoma I. **Inguinal** 1. Local infection 2. Diaper dermatitis 3. Syphilis

A good history and physical exam will go along way to help differentiate not only benign from malignant but also lymphadenopathy from other forms of neck masses that may resemble a lymph node.[26]

2. Age of the child

Some organisms have a predilection for specific age groups. *S. aureus* and group B streptococci have a predilection for neonates; *S. aureus* and group B streptococci, for infants; viral agents, *S. aureus*, group A β -hemolytic streptococci, and atypical mycobacteria for children from 1 to 4 years of age; and anaerobic bacteria, toxoplasmosis, cat-scratch disease, and tuberculosis for children from 5 to 15 years of age. Most children with cervical lymphadenitis are 1 to 4 years of age. The prevalence of various childhood neoplasms changes with age. In general, lymphadenopathy secondary to neoplasia increases in the adolescent age group [27].

3. Laterality and chronicity

Acute bilateral cervical lymphadenitis is usually caused by a viral upper respiratory tract infection or pharyngitis due to *S.* pyogenes[28,29]. Acute unilateral cervical lymphadenitis is caused by S. pyogenes or S. aureus in 40% to 80% of cases. The classical cervical lymphadenopathy in Kawasaki disease is usually acute and unilateral. Typically, acute suppurative lymphadenitis is caused by S. aureus or S. pyogenes[30]. Subacute or chronic cervical lymphadenitis is often caused by B. henselae , Toxoplasma gondii , EBV, CMV, non tuberculosis mycobacteria, and M. tuberculosis[28,29]. Less common causes include syphilis, Nocardia brasiliensis, and fungal infection.

4. Concurrent illness and past health

Preceding tonsillitis suggests streptococcal infection. Recent facial or neck abrasion or infection suggests staphylococcal infection. Periodontal disease might indicate infections caused by anaerobic organisms. A history of cat-scratch raises the possibility of *B. henselae* infection. A history of dog bite or scratch suggests specific causative agents such as *Pasteurella multocida* and *S. aureus*. Lymphadenopathy resulting from CMV, EBV, or HIV might follow a blood transfusion. The immunization status of the child should be determined. [31,32]

Constitutional symptoms such as fatigue, malaise, and fever, often associated with impressive cervical lymphadenopathy and atypical lymphocytosis, are seen most commonly with mononucleosis syndromes. Significant fever, night sweats, and unexplained weight loss of more than 10 percent of a patient's normal body weight are the "B" symptoms of Hodgkin's lymphoma.[26]

Symptoms such as arthralgias, muscle weakness, or unusual rash may indicate the possibility of autoimmune diseases such as rheumatoid arthritis, lupus erythematosus, or dermatomyositis. More specific review questions, such as whether pain occurs in the area of lymphadenopathy, may bring out a rare but fairly specific finding of a neoplasm such as Hodgkin's lymphoma.[33]

Associated symptoms Fever, sore throat, and cough suggest an upper respiratory tract infection. Fever, night sweats, and weight loss suggest lymphoma or tuberculosis. Recurrent cough and hemoptysis are indicative of tuberculosis. Unexplained fever, fatigue, and arthralgia raise the possibility of collagen vascular disease or serum sickness[30].

After a thorough history, a solid methodical physical exam is the next step. [12]

II. Physical examination

1. General

Malnutrition or poor growth suggests chronic disease such as tuberculosis, malignancy, or immunodeficiency.[27]

2. Associated signs

A thorough examination of the ears, eyes, nose, oral cavity, and throat is necessary. Acute viral cervical lymphadenitis is variably associated with fever, rhinorrhea, conjunctivitis, pharyngitis, and sinus congestion [27]. A beefy red throat, exudate on the tonsils, petechiae on the hard palate, and a strawberry tongue suggest infection caused by *S. pyogenes* . Unilateral facial or submandibular swelling, erythema, tenderness, fever, and irritability in an infant suggest group B streptococcal infection.[28]

Diphtheria is associated with edema of the soft tissues of the neck, often described as "bull-neck" appearance. The presence of gingivostomatitis suggests infection with HSV, whereas herpangina suggests infection with coxsackie virus[29]. Rash and hepatosplenomegaly suggest EBV or CMV infection[27]. The presence of pharyngitis, maculopapular rash, and splenomegaly suggest EBV infection. Conjunctivitis and Koplik spots are characteristics of rubeola. The presence of pallor, petechiae, bruises, sternal tenderness, and hepatosplenomegaly suggests leukemia.[33]

Prolonged fever, conjunctival infection, oropharyngeal mucous membrane inflammation, peripheral edema or erythema, and a polymorphous rash are consistent with Kawasaki disease.[34]

3. Characteristics of the lymph tissue

All accessible node-bearing areas should be examined to determine whether the lymphadenopathy is generalized. The nodes should be measured for future comparison.[28]

Fluctuation in size of the nodes suggests a reactive process, whereas relentless increase in size indicates a serious pathology . Tenderness, erythema, warmth, mobility, fluctuance, and consistency should be assessed.[35]

The location of involved lymph nodes often gives clues to the entry site of the organism and should prompt a detailed examination of that site. Submandibular and submental lymphadenopathy is most often caused by an oral or dental infection, although this feature may also be seen in cat-scratch disease and non-Hodgkin's lymphoma. Acute posterior cervical lymphadenitis is classically seen in persons with rubella and infectious mononucleosis.[28,29]

Supraclavicular or posterior cervical lymphadenopathy carries a much higher risk for malignancy than does anterior cervical lymphadenopathy.

Cervical lymphadenopathy associated with generalized lymphadenopathy is often caused by a viral infection. Malignancies (eg, leukemia or lymphoma), collagen vascular diseases (eg, juvenile rheumatoid arthritis or systemic lupus erythematosus), and some medications are also associated with generalized lymphadenopathy. In lymphadenopathy

resulting from a viral infection, the nodes are usually bilateral and soft and are not fixed to the underlying structure. When a bacterial pathogen is present, the nodes can be either unilateral or bilateral, are usually tender, might be fluctuant, and are not fixed. The presence of erythema and warmth suggests an acute pyogenic process, and fluctuance suggests abscess formation. A “cold” abscess is characteristic of infection caused by mycobacteria, fungi, or B. henselae .[36-38]

In patients with tuberculosis, the nodes might be matted or fluctuant, and the overlying skin might be erythematous but is typically not warm. Approximately 50% of patients with lymphadenitis caused by nontuberculosis mycobacteria develop fluctuance of the lymph node and spontaneous drainage; sinus tract formation occurs in 10% of affected patients . In lymphadenopathy resulting from malignancy, signs of acute inflammation are absent, and the lymph nodes are hard and often fixed to the underlying tissue.[27,39]

Generally, lymph nodes that are hard and painless have increased significance for malignant or granulomatous disease and typically merit further investigation. For example, the nodes of nodular sclerosing Hodgkin's lymphoma are firm, fixed, circumscribed, and rubbery. This is in contrast to viral infection, which typically produces hyperplastic nodes that are bilateral, mobile, nontender, and clearly demarcated. Painful or tender lymphadenopathy is non-specific but typically represents nodal inflammation from an infection. In rare cases, painful or tender lymphadenopathy can result from hemorrhage into the necrotic center of a neoplastic node or from pressure on the nodal capsule caused by rapid tumor expansion.Therefore the presence or absence of tenderness does not reliably differentiate benign from malignant nodes.[40,41]

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.[34]

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 or sarcoidosis) or malignant (e.g., lymphomas or metastatic carcinoma).[40]

Unfortunately, there is no single clinical feature that can predict the histologic diagnosis of a biopsied lymph node, but the features listed in Table 3 are more likely to be present when a more serious condition is triggering the lymphadenopathy. If an enlarged node has increased in size after 2 weeks of monitoring or the node has not decreased in size by 4 to 6 weeks or returned to normal size by 8 to 12 weeks, then a biopsy is recommended if the diagnostic evaluation thus far has been unrevealing.[42]

III. Differential diagnosis of cervical lymphadenopathy will include

Cervical masses are common in children and might be mistaken for enlarged cervical lymph nodes. So, the differential diagnosis of cervical lymphadenopathy is important to be known. In general, congenital lesions are painless and are present at birth or identified soon thereafter.

1. Mumps
2. Thyroglossal cyst
3. Branchial cleft cyst
4. Sternomastoid tumor
5. Cervical rib
6. Cystic hygroma
7. Hemangioma
8. Laryngocele
9. Dermoid cyst

Clinical features that may help distinguish the various conditions from cervical lymphadenopathy are:

1. **Mumps.** The swelling of mumps parotitis crosses the angle of the jaw.On the other hand, cervical lymph nodes are usually below the mandible
2. **Thyroglossal cyst** is a mass that can be distinguished by the midline location between the hyoid bone and suprasternal notch and the upward movement of the cyst when the child swallows or sticks out his or her tongue.
3. **Branchial cleft cyst.** A branchial cleft cyst is a smooth and fluctuant mass located along the lower anterior border of the sternomastoid muscle.
4. **Sternomastoid tumor.** A sternomastoid tumor is a hard, spindle-shaped mass in the sternomastoid muscle resulting from perinatal hemorrhage into the muscle with subsequent healing by fibrosis . The tumor can be moved from side to side but not upward or downward. Torticollis is usually present.
5. **Cervical ribs.** Cervical ribs are orthopedic anomalies that are usually bilateral, hard, and immovable. Diagnosis is established with a radiograph of the neck.
6. **Cystic hygroma.** Cystic hygroma is a multiloculated, endothelial-lined cyst that is diffuse, soft, and compressible, contains lymphatic fluid, and typically transilluminates brilliantly.
7. **Hemangioma.** Hemangioma is a congenital vascular anomaly that often is present at birth or appears shortly thereafter. The mass is usually red or bluish.
8. **Laryngocele.** A laryngocele is a soft, cystic, compressible mass that extends out of the larynx and through the thyrohyoid membrane and becomes larger with the Valsalva maneuver. There might be associated stridor or hoarseness, and a radiograph of the neck might show an air fluid level in the mass.
9. **Dermoid cyst.** A dermoid cyst is a midline cyst that contains solid and cystic components; it seldom transilluminates as brilliantly as a cystic hygroma, and a radiograph might show that it contains calcifications.[26,28]

There are 3 clinical findings to differentiate patients whose nodal biopsy results lead to a treatable diagnosis from patients whose biopsy results did not. The 3 clinical findings included lymph node size greater than 2.0 cm; absence of ear, nose, and throat symptoms; and presence of an abnormal chest radiograph.[43]

The definitive test for ruling out the most feared diagnosis, cancer, is a biopsy of the enlarged lymph node. Table 2 lists the features that should prompt referral for lymph node biopsy. The presence of only one feature may or may not require immediate attention, but a combination of features makes the situation more critical. A persistent node, despite a trial of antibiotics, or lymphadenopathy associated with worrisome systemic signs and symptoms will need a biopsy sooner than later. In particular, the presence of supraclavicular adenopathy, fever, arthrlagias, and weight loss should spark the clinician to refer the patient for a biopsy for definitive diagnosis.(44)

Table (2): Features prompting a possible biopsy* (29)

• Node size greater than 2.0 cm
• Node increasing in size over 2 weeks
• No decrease in node size after 4–6 weeks
• Node not returned to baseline size after 8–12 weeks
• No decrease in size despite one or two antibiotic trials
• Absent ears, nose, and throat symptoms
• Abnormal chest radiograph
• Presence of a supraclavicular node
• "Rubbery" consistency to the node
• Presence of systemic signs and symptoms
Fever
Weight loss
Arthralgia
Hepatosplenomegaly
*A feature may or may not indicate the biopsy of lymph node, a combination may.

The anatomic location of localized adenopathy will sometimes be helpful in narrowing the differential diagnosis. For example, infectious mononucleosis causes cervical adenopathy.(41)

IV. 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. 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.(45)

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.(45)

For most patients who present with acute, unilateral lymphadenopathy minimal workup is necessary. Many patients will get a CBC with differential. Subacute disease or disease that is not responding to therapy needs to be further evaluated. Common laboratory tests are as follows: ESR, Rapid Streptococcal test, serology (EBV, Toxoplasmosis, CMV,

Syphilis, and HIV), PPD placement, urine VMA and LDH. Many of these tests are self explanatory however others can be very specific to disease processes. ESR may be significantly elevated in Kawasaki disease. A PPD test is often positive in patients with mycobacterial lymphadenitis regardless being tuberculous or non-tuberculous. Urine VMA can be elevated in children with neuroblastoma and while LDH is often elevated in lymphoma.(16)

Imaging can include CXR, CT, MRI, Ultrasound, ECHO, and finally biopsy. CXR is useful for patients in whom systemic disease is suspected and can be helpful in identifying cavitary TB lesions and even mediastinal lymphadenopathy. CT, MRI, and ultrasound can all be used to evaluate for abscess formation and to follow the progress of an abscess after it forms, however ultrasound is probably the better choice to decrease the amount of radiation and resources spent performing the study. EKG and ECHO are also commonly used in patients suspected of having Kawasaki disease.(46)

Ultrasound is an ideal imaging tool for initial assessment of cervical lymph nodes in children. Grey scale ultrasound helps to evaluate the morphology of cervical nodes, whereas power Doppler ultrasound assesses the nodal vasculature. On grey scale ultrasound, useful sonographic features that help in identifying pathologic nodes include round contour, absence of echogenic hilus, intranodal necrosis, calcification, ill-defined borders, matting, and adjacent soft tissue edema.(47)

On color Doppler ultrasound, evaluation of vascular pattern of lymph nodes helps to differentiate malignant and benign nodes. Ultrasound-guided fine-needle aspiration cytology is becoming popular in paediatric patients, and ultrasound-guided core biopsy is also possible in this group of patients under local anaesthesia. (17)

Reactive lymphadenopathy had the following characteristics; size less than 1 cm, oval shape with short:long ratio less than 0.5, normal hilar vascularity, and a low resistive index with high blood flow when using Doppler technology. Malignant lymphadenopathy had the characteristics of being greater than 1cm, round with a short:long ratio greater than 0.5, necrotic center, no echogenic hilus, a high resistive index with low blood flow, and the ability to identify extracapsular spread. Using these parameters they found a sensitivity of 95% and a specificity of 83% success rate of differentiating reactive from malignant lymph nodes.(18)

Sonographic evaluation combined with the serum levels of LDH and sIL-2r is thus considered to be useful for determining the need to perform a biopsy.(21)

The Role of Biopsy:

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.(48)

Malignancy in lymph nodes may be difficult to assess, particularly in the early stages when they appear as small blue round cells. There is a real risk of malignancy and specialised tests such as immunostaining and flow cytometry remain useful adjuncts.(49)

Fine Needle Aspiration

Its major value is probably in establishing metastatic spread from a known tumour and providing material for culture.(50)

Surgical Lymph Node Biopsy

Lymph node biopsy remains an important and valuable surgical diagnostic tool in the evaluation of lymphadenopathy with very minimal risk to the patient . It allows the assessment of gland architecture in addition to the cytological features, thereby allowing for early diagnosis. It should be the endpoint of all cases of lymphadenopathy where a diagnosis is not readily forthcoming.(51)

The node sampled should be a representative node, preferably from a deep site. The node should be divided into specimens for histology and specimens for tissue culture (and TB culture). The specimen for histology should be further divided into a formalin fixed section and a section sent fresh for imprinting. (51)

Although fine needle aspiration has such a low sensitivity and high false negative rate it should still be the first line biopsy due to its relative ease and ability to be performed without general anesthesia. If FNA is inconclusive or negative, however, and suspicion is still high for malignancy, excisional biopsy should be performed. Throughout the literature excisional biopsy is considered the gold standard. The biopsy must be carried out so that the largest and firmest node palpable node is excised with the capsule intact. This prevents seeding in the case of malignancy or bacterial pathogens.(52)

The core-needle biopsy represents a safe and cheap alternative to the established ways of tissue sampling. As the histologic architecture of the lesion is preserved, it provides a sample that is adequate for histopathologic as well as immunohistochemical examination.(53-55)

This technique has been used very successfully by interventional radiologists for many years but has found little attention in the head and neck region and in pediatrics so far.(56,57)

Core-needle biopsies feature the advantages of open surgical biopsies without having their disadvantages. The automatic firing system is technically simpler, faster, and easier to perform than the traditional needle aspiration. The rapid action of the cutting needle has reduced the risk of needle deflection, patient movement during the procedure, patient discomfort, and fragmentation of the samples. Nevertheless, automatic core biopsy systems have found little attention in the head and neck region as yet. (58,59)

This may be due to the concern to use an automated spring-loaded cutting-needle biopsy-gun in an anatomic region, which comprises numerous large vessels and major nerves. Reviewing the international medical literature, we foundonly a few reported series evaluating the usefulness of core-needle biopsy devices in the head and neck. [58-61]

Patients should be cautioned to remain alert for the reappearance of the nodes because lymphomatous nodes have been known to temporarily regress.[41]

However, it should be remembered that a single biopsy may not give the definitive answer and long-term monitoring and further evaluation of the patient may be necessary or bone marrow aspiration maybe required to determine the etiology of the lymphadenopathy. Children with persistently enlarged nodes and negative workup should still be observed closely, possibly over years, with repeated physical examinations to determine if the node is regressing or if any new worrisome signs or symptoms are emerging. The exact etiology of lymphadenopathy may not be ascertained in over 40% to 50% of all cases, despite extensive investigations including biopsy.[24, 43]