

Overview of Lymphadenopathy Causes and Diagnosis

Baraa Faiez Rajab^{1*}, Doaa Izzeldin Elsheikh Abdalla², Mustafa Mohammed Fadlalla Mohammed³, Abdulaziz Jaber Alamri⁴, Abdullah Nabil Attar¹, Mohammed Ahmed Alghamdi⁵, Tarik Abdulrahman Hobani⁶, Mutaz Abdalhakam Abdalazez Taha⁷, Khalid Abdulaziz Balbaid⁸, Saleh Ghormallah Alghamdi⁹, Emad Ahmed Ezzalddin¹, Lojein Faisal Ahmed Alnomari¹⁰ and Wid Ameer Nawab⁶

¹King Abdulaziz Hospital, Jeddah, Saudi Arabia

²Renew Clinics, Jeddah, Saudi Arabia

³King Saud Medical City, Riyadh, Saudi Arabia

⁴Umm Al Qura University, Makkah, Saudi Arabia

⁵Al-Baha Univeristy, Al-Baha, Saudi Arabia

⁶East Jeddah General Hospital, Jeddah, Saudi Arabia

⁷Derriford Hospital, Plymouth, England, UK

⁸Dhurma General Hospital, Dhurma, Saudi Arabia

⁹King Abdulaziz University, Jeddah, Saudi Arabia

¹⁰Ibn Sina National College Collage, Jeddah, Saudi Arabia

***Corresponding Author:** Baraa Faiez Rajab, Consultant General Medicine, King Abdulaziz Hospital, Jeddah, Saudi Arabia.

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Abstract

Introduction: A wide variety of diseases can manifest as lymphadenopathy or swollen lymph nodes. When encountering a case of lymphadenopathy, certain diagnostic considerations include the age of the individual person, location of the pathology, duration of illness, and any associated symptoms. The critical task is to differentiate between benign, malignant, and any other condition requiring specific management. The differentiation is based on clinical, radiological, and histological investigations.

Aim of Work: The aim of this study is to overview lymphadenopathy.

Materials and Methods: This review is a comprehensive search of PUBMED from the year 1974 to 2021.

Conclusion: Since lymph nodes behave like the police stations of our body, lymphadenopathy involves a wide range of diseases. Several considerations influence both the incidence and prognosis of lymphadenopathy. In general, lymphadenopathy occurs more commonly among children and in the cervical region. The size and shapes of lymph nodes on radiographic imaging can suggest possible disease-causing lymphadenopathy. Further diagnostic evaluation, if needed, is done by FNAC, but excisional biopsy is considered the gold standard. A plethora of investigations comprising of history taking, physical exam, imaging, lab work, and finally, a biopsy may decide the possible treatment plan.

Keywords: Lymphadenopathy; Lymph Node; Ultrasound; Computed Tomography; FNAC; Biopsy; Malignancy

Introduction

Our body is equipped with a complex network of nodes, vessels and organs that are part of the immune system and compliments the circulatory system known as the lymphatic system. In the lymphatic system, lymph nodes are small glands present all over the body

where lymph is filtered and lymphocytes are housed. Lymphadenopathy is the enlargement of lymph nodes with either a known or an unknown etiology. On the other hand, the term “lymphadenitis” is generally used to indicate lymph node infections by microbial agents leading to inflammation. Lymphadenopathy causes either the growth of one compartment or hyperplasia of one or more cells that prevail over others [1].

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Etiology

The potential etiology for lymphadenopathy ranges from microbial infections, autoimmune pathosis, malignancy, and lymphoproliferative diseases. A wide range of infectious agents includes bacterial, fungal, viral, mycobacterial, spirochetal and protozoal organisms. Infectious lymphadenitis clinically presents with tender and painful swelling; fever and malaise may also be present [2].

Autoimmune diseases affecting the lymph nodes are sarcoidosis, amyloidosis, systemic lupus erythematosus, rheumatoid arthritis and eosinophilic granulomatosis with polyangiitis. Malignancy includes lymphoma, leukemia and metastatic cancer such as from the head and neck, and breast. Differentiating malignant lymph nodes from benign ones is imperative in clinical practice. Malignant lymph nodes are usually hard, rubbery and fixed. Lymphoproliferative disorders are a kind of disease where lymphocytes abnormally proliferate into monoclonal lymphocytes [2].

Pathophysiology

The primary characteristic of lymphadenopathic pathology is its inflammation of lymph nodes. This is due to increased inflow of lymphocytes into the nodes than their rate of outflow from the node. As seen from the physiology diagram, Fluid collected from the body travels via lymphatic vessels into lymph nodes for filtration of foreign antigens. Lymphoid cells meet foreign antigens and proliferate in number. An increase in the number of cells can cause capsule expansion which may result in pain. Lymph node follicles can also necrose due to infections or malignancy. Infiltration of neutrophils suggests bacterial infection, whereas lymphocyte infiltration may suggest viral etiology [4].

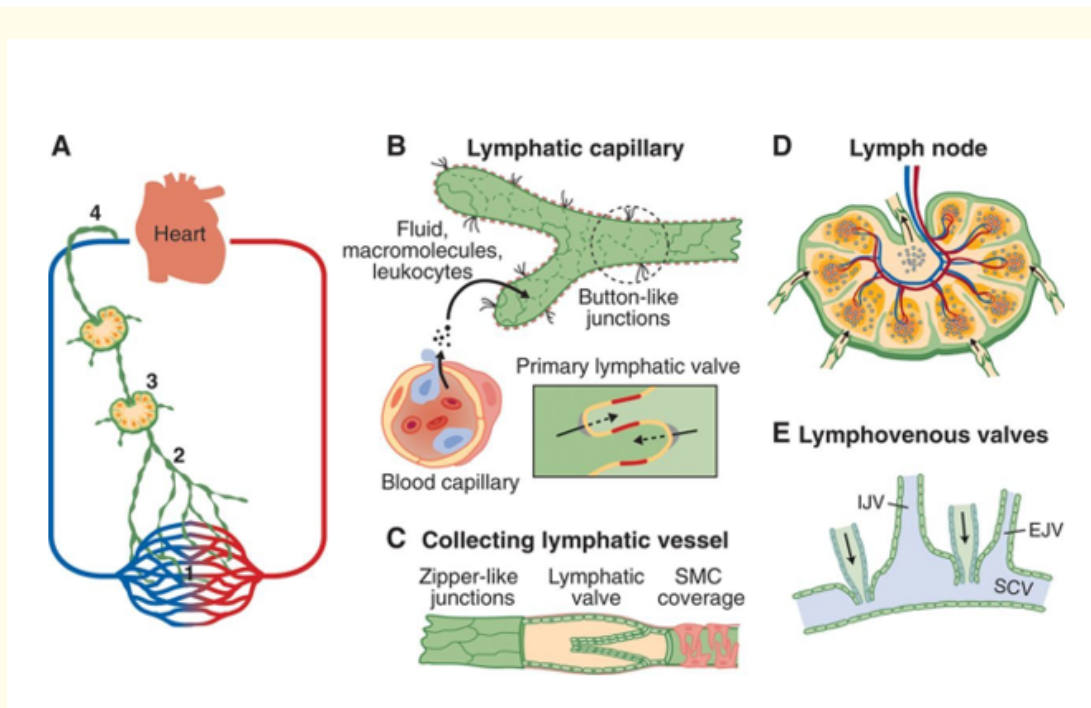


Figure 1: Basic physiology of lymphatic system [3]. A: Flow of lymphatic vascular system, B: Lymphatic capillaries absorb interstitial solutes, macromolecules, and lymphocytes from the vascular system. C: Collecting lymphatic vessels D: Lymph node with afferent and efferent vessels. E: Lymph drains into external/internal jugular veins and subclavian [3].

Consideration in lymphadenopathy [5]

Age

Children tend to have more lymphadenopathy than adults, especially in the cervical region, as they commonly get viral upper respiratory tract infections or streptococcal pharyngitis [6].

Age
Location
Length of time present
Associated signs and symptoms
Generalized lymphadenopathy
Extranodal associations
Splenomegaly and fever

Most lymphadenopathies are benign in nature and even more so in the younger population. Chronic, hard, and fixed lymphadenopathy in people older than 50 warrants a biopsy as they are likely to be malignant [7].

Size and shape

Lymph nodes (LN) greater than 1 cm or 10 mm in short axis diameter are judged malignant. Benign LN is usually ovoid in shape and becomes rounder due to infiltration of malignant cells. Benign LN is hypoechoic to adjacent muscle on ultrasonography and has echogenic fatty hilum. Malignancy features include loss of echogenic nodal hilum, irregular nodal contour, and internal nodal heterogeneity [8].

Location

Up to 600 lymph nodes exist within our body; most aren't palpable unless diseased. Lymphadenopathy is considered generalized if two or more noncontiguous areas are concerned and localized if only one area is concerned. Most cases are localized and that too in the head and neck region of the body [9].

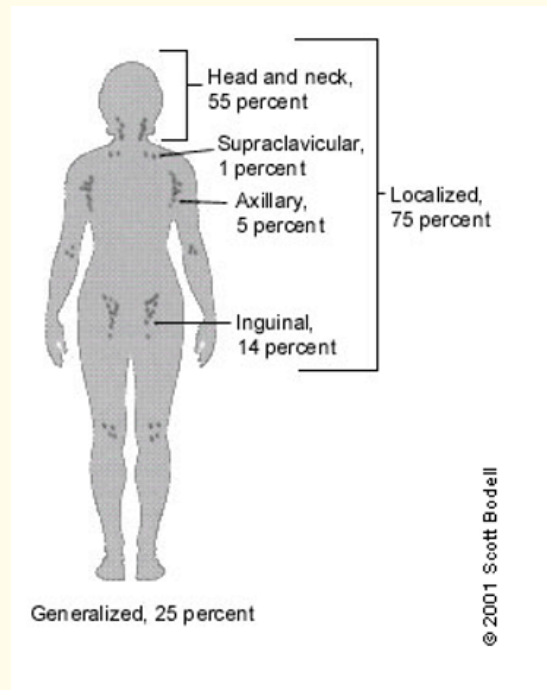


Figure 2: Showing the occurrence of lymphadenopathy by anatomic location [9].

Incidence

James W Moor, *et al.* 2008 reviewed cases of 342 superficial LN biopsies, out of which the distribution was cervical 63% (216 of 342), inguinal 22% (76 of 342), and axillary 17% (50 of 342). 34% were diagnosed with malignancy, 45% were benign and 15% were tuberculosis [10]. These results may mislead us to believe that up to 1/3rd of lymphadenopathies may be malignant. Fijten GH, *et al.* 1988 reported 0.6% of unexplained lymphadenopathy in the general population per year. They also studied 2,556 patients who reported to their family doctors for unexplained lymphadenopathy, of which 82 (3.2%) underwent biopsy, and 29 (1.1%) were diagnosed with malignancy. This shows that the incidence of malignant lymphadenopathy is rather rare [11].

Clinical history and examination

History involves:

- History of presenting illness
- Review of systems
- Past medical history: HIV, cancer history, History of Hodgkin's lymphoma
- Medications: Cephalosporins, phenytoin
- Sexual history: Sexually transmitted history
- Surgical history: Post-operative lymphadenopathy.

Physical exam:

- Vital signs: Fever may be present in infections
- Full body visual examination for signs of edema, infections, and lesions.
- Palpation of possible swollen LN: check for size, firmness, and tenderness [2].

Diagnostic evaluation

A general blood picture and serological examination in a laboratory should be done to rule out certain etiological factors [2].

Imagings

Ultrasound: Normal reactive lymph nodes are usually lesser than 1 mm in size, hypoechoic compared to adjacent muscles, oval in shape, and have echogenic fatty hilum. Malignancy features of LN include loss of echogenic nodal hilum, irregular nodal contour, and internal nodal heterogeneity [12].

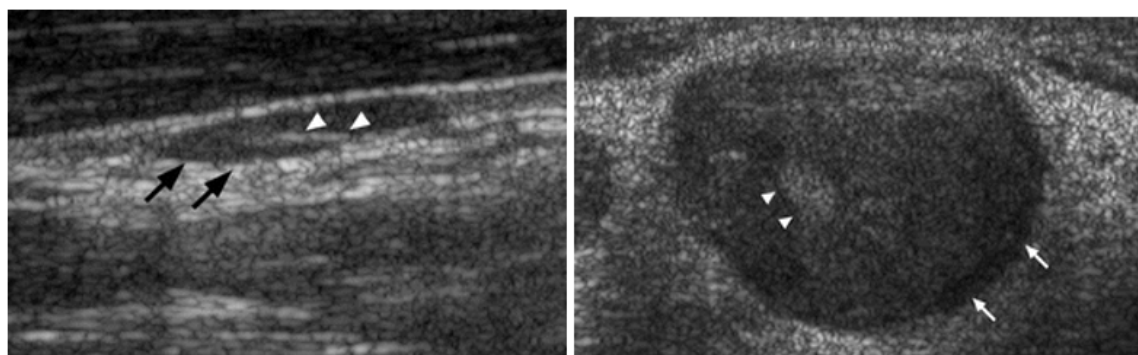


Figure 3: A: Normal lymph node (USG) [12]. B: Metastatic Lymph node (USG) [12].

A tuberculous LN is hypoechoic, round, and without echogenic hilus. They also show intra-nodal cystic necrosis, matting on nodes, and edema in adjacent soft tissues. In some lymphoproliferative diseases like Kikuchi's and Kimura's, nodes on USG appear similar to reactive LN [12].

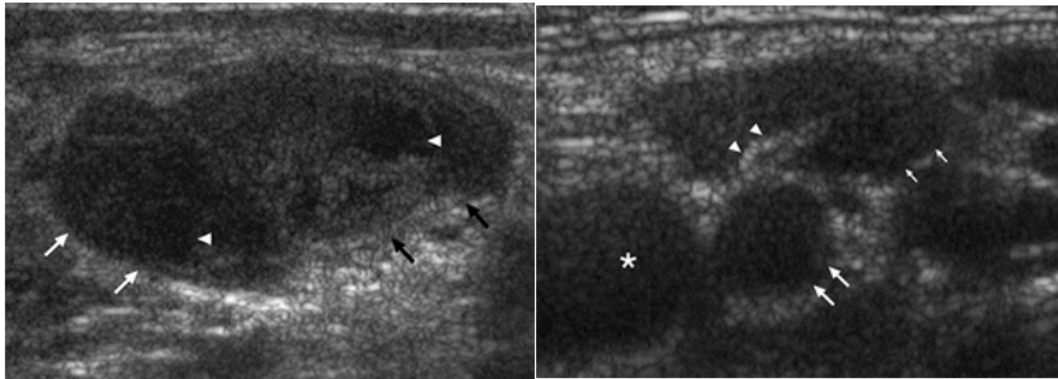


Figure 4: C: Tuberculous LN (USG) [12]. D: Kikuchi's disease LN (USG) [12].

CT (Computed tomography)

Computed tomography has been considered the gold standard for radiological examination of cancers. The diagnostic criteria for LN imaging through CT are based on size, shape, margin, density and enhancement patterns. There exists some dispute regarding the size of the LN that should be considered metastatic. Despite the lack of consensus, CT is considered the gold standard for identifying all the LNs from other structures so that surgeons can operate better. Also, sentinel node biopsy is relied upon subcutaneous injection of contrast agent and scanning with CT [13].

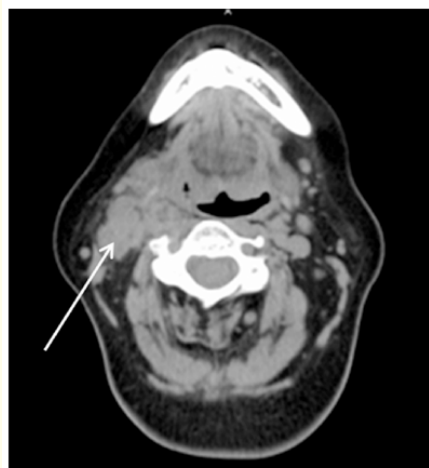


Figure 5: CT showing enlarged level II lymph nodes in the right neck (arrow) [14].

Biopsy and histopathology

Fine needle aspiration cytology (FNAC)

It is a rapid, inexpensive and minimally invasive diagnostic tool for the cytological examination of nodal parenchyma. It is especially indicated for the biopsy of surgically inaccessible lymph nodes. Although considered fairly reliable, they do miss out on accuracy. Nasreen H Hafiz, *et al.* 2011 performed a retrospective study on 157 patients who had undergone FNAC for cervical lymphadenopathy where histopathological results were compared with the same surgically excised LN. They found the diagnostic accuracy of FNAC for cervical lymphadenopathy to be 82.2% [15].

Excisional biopsy

Excisional biopsy and its histopathological examination are considered the gold standard for diagnosing the pathology associated with LN. History taking, physical exams, imaging, and FNAC can rule out various etiology and narrow down our search for potential malignancies. Older age, multiple lymphadenopathy, fixed LN with a rubbery texture, characteristic malignant features on CT and USG and undiagnosed FNAC reports all warrant an excisional biopsy. Ezra Ozkan, *et al.* 2015 evaluated 185 lymph node biopsy specimens and found malignancy in 123 (66.5%) of them. Therefore, suspected LN pathologies must be surgically excised for a histopathological exam [16].

Histological findings associated with lymphadenopathy:

- **Bacterial lymphadenitis:** Neutrophilic infiltrate within the sinus and medullary cords. Follicular hyperplasia also can be present.
- **Viral lymphadenopathy:** Macrophagic infiltrate and lymphoid hyperplasia.
- **Sarcoidosis:** Non-caseating granulomas replaces the normal architecture of the lymph node
- **Non-Hodgkin lymphoma:** Follicular pattern shows uniform nodularity with uniform shape and size, whereas diffuse pattern shows normal architecture with small lymphocyte infiltration.
- **Hodgkin's lymphoma:**
 1. Nodular sclerosing
 2. Mixed cellularity
 3. Lymphocyte-rich
 4. Lymphocyte-depleted [2].

Sentinel node biopsy: Sentinel lymph node (SLN) is the first LN to receive drainage from a tumor. A tracer/dye/radioisotope is injected around the tumor site, and labeled LN are surgically excised and histologically studied for the presence of disease. The tumor-laden or tumor-free status can save the patient from more aggressive surgery [17].

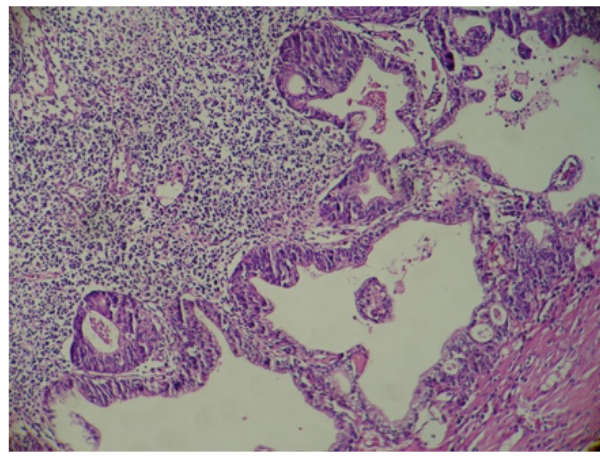


Figure 6: Metastatic cervical lymph node of primary squamous cell carcinoma [18].

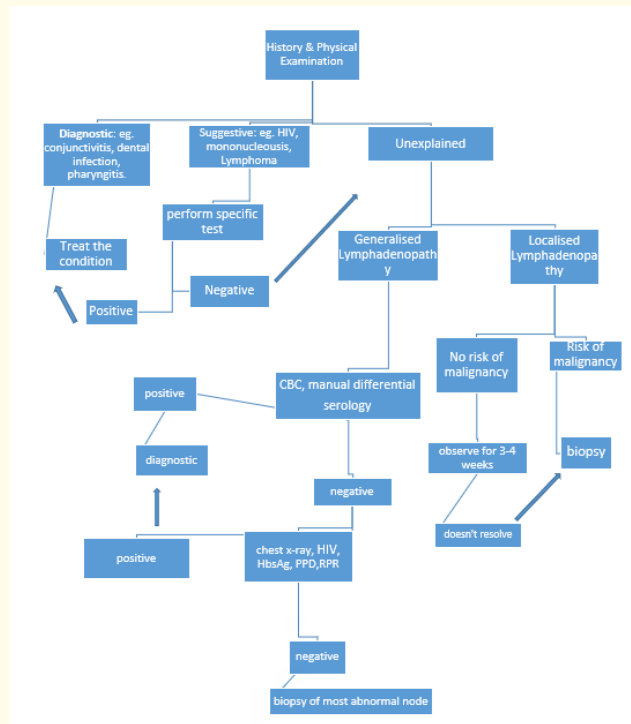


Figure 7: Algorithm for the evaluation of a patient with lymphadenopathy and treatment plan (HIV: Human Immunodeficiency Virus; CBC: Complete Blood Count; PPD: Purified Protein Derivative; RPR: Rapid Plasma Reagin; ANA: Antinuclear Antibody; HBsAg: Hepatitis B Surface Antigen) [19].

Treatment

Treatment of lymphadenopathy can range from just observation to surgery, radiotherapy, etc. It depends on the underlying condition causing the lymphadenopathy:

- Infections: Antibiotics, antivirals and antifungals
- Autoimmune: Systemic steroids
- Malignancy: Surgery, radiation and chemotherapy
- Drugs: Discontinue drugs and re-evaluate treatment [2].

Conclusion

Since lymph nodes behave like the police stations of our body, lymphadenopathy involves a wide range of diseases. Several factors influence both the incidence and prognosis of lymphadenopathy. In general, lymphadenopathy occurs more commonly among children and in the cervical region. The size and shapes of lymph nodes on radiographic imaging can suggest possible disease-causing lymphadenopathy. Further diagnostic evaluation, if needed, is done by FNAC, but excisional biopsy is considered the gold standard. A plethora of investigations comprising of history taking, physical exam, imaging, lab work and finally, a biopsy may decide the possible treatment plan.

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