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CLINICOPATHOLOGICAL ASSESSMENT OF CERVICAL LYMPHADENOPATHY IN A SAMPLE OF IRAQI PATIENTS

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ABSTRACT

Background: Lymphadenopathy is a pathological process of lymph nodes manifested by abnormally increased size or altered consistency or number. Cervical Lymphadenopathy refers to cervical nodal tissue measuring more than one cm in diameter. It may be classified according to its etiology into reactive and neoplastic. Cervical lymph nodes are a common site of metastases for malignant tumors from other sites; these include upper aerodigestive tract, post nasal and supraclavicular regions. Cervical LAP is further classified into acute (2 weeks duration), subacute (2–6 weeks duration), and chronic (does not resolve by 6 weeks). **Objective:** To assess the correlation of various clinicopathological parameters of cervical lymphadenopathy with final histopathological diagnosis. Clinicopathological parameters include (Age, Sex, Duration, Clinical presentation, Site, Gross finding, Neoplastic or non-neoplastic diagnosis, Primaryneoplasm (lymphoma) vs. secondary (metastatic), histopathological diagnosis. **Materials and Methods:** A retrospective analysis of 160 randomly chosen patients with cervical lymphadenopathy who were gathered from the Teaching Laboratory of Al Imamain Al-Kadhimain Medical City, the Pathology Departments of Ghazi Al Hariri Surgical Specialties Teaching Hospital, and Teaching laboratories of medical city between January 2024 and December 2024, the samples were collected between January 2018 to December 2023. The slides and histopathology reports for each case were revised and reexamined. The pathology reports of the patients were also used to extract the clinical parameters. Inclusion criteria were patients with cervical lymphadenopathy while samples with insufficient patient data were excluded. **Results:** The study analyzed the distribution of cervical lymphadenopathy among 160 patients, revealing that the most common age groups were <20 and >50 years, with a mean age of 31 years. Male patients slightly outnumbered females, with a male- to-female ratio of 1.46:1. The most frequent clinical presentation was lymphadenopathy accompanied by systemic symptoms such as fever, weight loss, and night sweats (43.8%), with 78.7% of cases having a chronic duration. Level IV of the cervical lymph nodes demonstrated the highest frequency of lymphadenopathy (22.5%). Most enlarged lymph nodes measured 2–5 cm (66.25%), with 59.4% of cases showing multiple node involvement .Grossly, 53.68% of lymph nodes were discrete, and 62.5% exhibited firm consistency. Reactive lymphadenopathy was the most common cause (35%), followed by tuberculosis. (%17.5)Among lymphomas, Hodgkin lymphoma accounted for 15% of cases, with mixed cellularity (45.83%) being the most frequent subtype, followed by nodular sclerosis (37.5%). Non-Hodgkin lymphoma represented (%11.9) of cases, with diffuse large B-cell lymphoma being the predominant subtype (47.4%). Metastatic lymphadenopathy was diagnosed in (17.5%) of cases, with papillary thyroid carcinoma (35.6%) and squamous cell carcinoma of the lung (25%) being the most frequent sources of metastases. **Conclusion:** Majority of cervical lymphadenopathy in the current study are benign. Reactive follicular hyperplasia is the most commonly observed benign histological finding. Hodgkin lymphoma is the most prevalent form of lymphoma. Mixed cellularity emerged as the most common subtype of HL, followed by nodular sclerosis. Papillary thyroid carcinoma (PTC) was the most common primary malignancy that metastasized to cervical lymph nodes, followed by squamous cell carcinoma.

1.1 INTRODUCTION

Lymphadenopathy (LAP) is a pathological process of lymph nodes manifested by abnormally increased size or altered consistency or number.[1] Cervical lymphadenopathy refers to cervical nodal tissue measuring more than one cm in diameter.[2]

The enlargement of lymph nodes is an index of spread of infection and malignancy. Therefore, the proper and early diagnosis of lymphadenopathy is very important for starting of early and effective treatment. It is not a

disease by itself; rather, it is a sign of an underlying pathology that ranges from a trivial infection to a metastatic malignant neoplasm. Cervical lymphadenopathy may be classified according to its etiology into reactive and neoplastic. In General, cervical lymphadenopathy may be due to lymphoid hyperplasia or infiltration.[3]

Lymphoid hyperplasia is further sub classified, based on the anatomic and histopathology, into the following patterns:[1]

1. Reactive follicular hyperplasia.
2. Diffuse paracortical hyperplasia.
3. Sinus hyperplasia.
4. Mixed hyperplasia.
5. Acute nonspecific lymphadenitis.
6. Chronic nonspecific lymphadenitis.
7. Necrotizing lymphadenitis (granulomatous and non-granulomatous).

Lymph node may be infiltrated by malignant cells, in malignant lymphoma/leukemia, or by metastatic tumors, The former category includes a wide spectrum of lymphoid and hematopoietic neoplasms that are classified by the World Health organization (WHO) 2016 into:[4]

1. Precursor B and T cell neoplasm.
2. Mature B cell neoplasm.
3. Mature T cell and NK cell neoplasm.
4. Hodgkin's lymphoma.
5. Histiocytic and dendritic neoplasm.
6. Post-transplantation lymphoproliferative disorders (LPDs).

An additional pathological entity is spindle cell lesions of lymph node which include
(1) bacillary angiomatosis, (2) Kaposi sarcoma, (3) palisaded myofibroblastoma, and
(4) inflammatory pseudo tumor of lymph node.[5]

Cervical lymph nodes are a common site of metastases for malignant tumors from other sites; these include upper aerodigestive tract, post nasal and supraclavicular regions. Primary lymphoma in neck nodes must be considered in any differential diagnosis. Occasionally, neoplasms from primary sites outside of the head and neck region may unexpectedly metastasize to the neck.[6]

Cervical lymphadenopathy is further classified into acute (2 weeks duration), subacute (2–6 weeks duration), and chronic (does not resolve by 6 weeks). A wide range of causes can result in cervical lymphadenopathy.

A recent cross-sectional study has demonstrated that the most likely cause of cervical lymphadenopathy depends on the age group; reactive or nonspecific inflammation was the most common cause in those younger than 14 years; tuberculous lymphadenopathy was the predominant pathology in 14–59 year group, while cancer should be suspected if the patient is 60 years or older.[7]

1.2. Aim of the study

The aim of this study is to assess the correlation of various clinicopathological parameters of cervical lymphadenopathy with final histopathological diagnosis.

The following clinicopathological parameters will be studied (Age, Sex, Duration, Clinical presentation, Site, Gross finding including: size, single or multiple lymph nodes discrete or matted lymph nodes and consistency, Neoplastic or non-neoplastic diagnosis, Primary neoplasm (lymphoma) vs. secondary (metastatic) and histopathological subtype of primary and metastatic tumors.

2.1. Embryology

Lymph nodes develop from the lateral plate mesoderm, which grows on either side of intermediate mesoderm, they develop. First, at week five, huge central veins' endothelial outgrowths give rise to lymphatic sacs. Second, lymphatic sacs give rise to lymphatic plexus. Third, mesenchymal cells penetrate plexuses and multiply, clumping together to create lymph nodes. By the first trimester, small groups of lymphoblast are present by the second trimester, initial follicles are visible and the cortex can be distinguished from the medulla.[8]

2.2. Anatomical Considerations

Of the 800 lymph nodes (LNs) in the body, about 300 are located in the neck region. The path to a clinically sound classification was opened by Rouviere's thorough examination of LNs in 1932 and Lindberg et al.'s later demonstration of the metastatic propensity of head and neck cancers to certain LN areas. The cervical LNs' currently recognized level classification was created by the American Joint Committee on Cancer (AJCC) and the American Academy of Otolaryngology and Head and Neck Surgery (AAO-HNS).[9] The level classification of cervical lymphatics all illustrated in figure (2.1).

2.2.1. Labeling of the Cervical Lymph Node Levels

Level IA: **Submental Area:** These LNs are located inside the triangle formed by the inferior hyoid bone and the anterior belly of the digastric muscles on both sides.

Level IB: Submandibular Region: At these lymph nodes is located inside the triangle formed, inferiorly, by the digastric muscle's anterior and posterior bellies and superiorly, by the mandibular body. It is important to remember that if the LNs at this level are removed, the submandibular gland should also be taken with the samples. Level I nodes are susceptible to the spread of malignancies from the anterior nasal cavity, mouth cavity, soft tissues of the midface, and submandibular gland.[10][11]

Level IIA and IIB: Upper Jugular Group: These LNs encircle the internal jugular vein's upper third. They stretch from the superior base of the skull to the inferior border of the hyoid bone on the inferior side. Its anterior

boundary is formed by the stylohyoid and sternohyoid muscles' lateral borders. The sternocleidomastoid muscle's (SCM) rear border forms its posterior boundary. Level IIA LNs are located in front of the spinal accessory nerve's vertical plane, whereas Level IIB LNs are located in back of it. Radiologically, the vertical plane at the posterior portion of the submandibular gland divides the level IB and level IIA LNs.

The face, the parotid gland, the submandibular, submental, and retropharyngeal nodes all supply lymphatics to Level II.

Additionally, Level II directly receives the lymphatics that are collected from the middle ear, sublingual and submandibular glands, external auditory canal, larynx, pharynx, and nasal cavity.

Level IIa and IIb nodes may contain metastases from malignancies of the nasopharynx, oropharynx, larynx, hypopharynx, and major salivary glands, in addition to tumors of the nasal and oral cavities.[10][11]

Level IIb is less commonly linked to cancers of the oral cavity, larynx, or hypopharynx and more usually connected with primary tumors of the oropharynx or nasopharynx.

Level III: Middle Jugular Group: This level is situated approximately in the middle third of the intercostal space and stretches from the inferior border of the hyoid bone superiorly to the inferior border of the cricoid cartilage inferiorly. Once more, the lateral border of the sternohyoid muscle represents the anterior boundary, while the posterior border of the SCM represents the posterior limit. The juguloomohyoid LN is a member of this collective.

Level III gathers lymphatic drainage from the tonsils, larynx, hypopharynx, thyroid gland, and base of the tongue. Level III nodes may contain metastases from malignancies of the larynx, nasopharynx, oropharynx, hypopharynx, or oral cavity.[10][11]

IV - Lower jugular and medial supraclavicular
Level IVa and IVb are separated arbitrarily by a distance of 2 cm from the sternoclavicular joint cranially.

Level IVa; these nodes could be home to metastases from thyroid, cervical esophageal, laryngeal, and hypopharyngeal malignancies.

In rare instances, metastases from the anterior oral cavity may appear here with little or no proximal nodal disease.

Level IVb; these nodes may contain metastases from thyroid, cervical esophageal, subglottic laryngeal, and hypopharyngeal malignancies.[10][11]

V- Supraclavicular and posterior triangle, Level V includes the transverse cervical veins and the nodes of the posterior triangle group that are situated behind the sternocleidomastoid muscle, surrounding the lower segment of the spinal accessory nerve.

Level V nodes are primarily linked to primary malignancies of the thyroid gland, nasopharynx, oropharynx, and the cutaneous tissues of the posterior scalp.[10][11]

Level Vc: Cervical Level, The lateral supraclavicular nodes, which are found in the posterior triangle nodes (levels Va and Vb) that extend from the cervical transverse vessels to a point arbitrarily situated two centimeters cranially above the sternal manubrium, are contained in this level. Level Vc is more often linked to nasopharyngeal cancers and receives efferent lymphatics from the posterior triangle nodes (level Va and Vb).[10][11]

Level VI: Anterior cervical group
The deeper prelaryngeal, pretracheal, paratracheal, and recurrent laryngeal nerve nodes (level VIb) and the superficial anterior jugular nodes (level VIa) are located on this level.

VIa; the anterior jugular nodes, which are superficially situated, are found at this level.

VIb; this level lies in the space between the common carotid arteries' medial margins. Pre-laryngeal nodes in front of the larynx and cricoid pre-tracheal nodes in front of the trachea are the nodes in this region. Paratracheal nodes, also known as recurrent laryngeal nerve nodes, are located in front of the trachea.[10][11]

Level VII: VIIa; The retropharyngeal level, These nodes are located in the retropharyngeal area, and they stretch cranially from the massa lateralis, the upper margin of the first cervical vertebrae, to the caudal cranial edge of the hyoid bone. The pharyngeal constrictor muscles border this area from the front, while the longus capitis and longus colli muscles border it from the back. The internal carotid artery's medial border limits the retropharyngeal nodes laterally.

Efferent lymphatics from the soft palate, the Eustachian tube, and the nasopharyngeal mucosa are received by the retropharyngeal nodes.

These nodes may contain metastases from tumors of the oropharynx, which mostly affects the tonsillar fossa and soft palate, as well as cancers of the nasopharynx and posterior pharyngeal wall.[10][11]

VIIb; Retrostyloid, The level II nodes continue cranially into the retro-styloid nodes. They can be found in the adipose tissue surrounding the jugulo-carotid arteries and extending to the jugular foramen at the base of the skull.[10][11]

Level VIII: the parotid group

The subcutaneous pre-auricular nodes, the superficial and deep intraparotid nodes, and the sub parotid nodes are all part of the parotid node group, which is located on this level. These nodes reach the mandible from the external auditory canal and the zygomatic arch. They stretch from the posterior edge of the masseter and pterygoid muscles anteriorly to the anterior edge of the sternocleidomastoid muscle and the posterior belly of the digastric muscle posteriorly. They also extend from the subcutaneous tissue laterally to the styloid process medially.

The frontal and temporal skin, eyelids, conjunctiva, auricle, external auditory meatus, tympanum, nasal cavities, root of the nose, nasopharynx, and Eustachian tube all supply lymph to the parotid group. They may be harboring metastases from orbital, nasal cavities, parotid gland, external auditory canal, and frontal and temporal skin malignancies.[10][11]

Level IX: Buccofacial

The malar and bucco-facial node group, which includes sporadic superficial lymph nodes around the facial arteries on the buccinator muscle's external surface, is located in Level IX.

These nodes reach level Ib at the caudal edge of the mandible, which is caudally extended from the caudal edge of the orbit (cranially). They extended from the anterior border of the masseter muscle and the Bichat's fat pad (posteriorly) to the anterior subcutaneous tissue of the face, lying on the buccinators muscle (medially) in the subcutaneous tissue.

The nose, eyelids, and cheek send efferent vessels to the bucco-facial nodes. They could potentially be harboring metastases from tumors that have spread to the nose, cheek soft tissue, the maxillary sinus, the buccal mucosa, and the skin of the face.[10][11]

Level X - Retroauricular and occipital

The retroauricular (also known as mastoid) and subauricular nodes are located in Level Xa. The subauricular nodes consist of superficial nodes that are situated on the mastoid process from the cranial margin of the external auditory canal cranially to the tip of the mastoid at the caudal direction.

The cranial and superficial continuation of the level Va nodes up to the cranial protuberance are the occipital lymph nodes, found in level Xb. They extend from the anterior (lateral) border of the trapezius muscle to the posterior border of the sternocleidomastoid muscle.

Skin malignancies of the occipital area (Xb) and the retro-auricular area (Xa) are the causes of lymph node metastases in level X.[10][11]

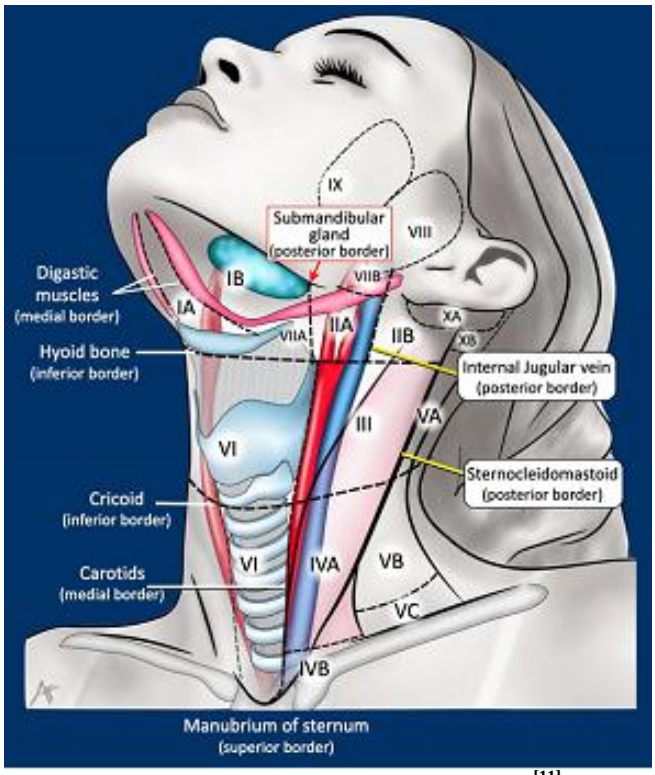

Figure (2:1) cervical lymph nodes map.[11]

2.3. Histology of lymph nodes The cortex

Robust connective tissue, consisting of collagen and elastin fibers with scattered fibroblasts, surrounds lymph nodes. Many afferent lymph vessels puncture the lymph nodes convexed surface. Through the trabecular extensions of the cortex, they reach the deeper regions of

the lymph node.[12]

The trabeculae continue as reticulin Fibrils (type III collagen) as they pass into the lymph node, providing the gland with more structural support.

The cortex is the outermost layer. It consists of lymphoid nodules, a cortical sinus, and a subcapsular sinus. The first area of the node into which lymph fluid from the afferent channels enters is the subcapsular sinus. After that, the fluid moves on to the cortical sinuses, which are the subcapsular sinus's branches. Because the cortical sinuses move along the lymph node's trabecular network, they are often referred to as trabecular sinuses.

Both reticulin fibers and dendritic processes puncture the endothelium of the trabecular sinuses. Through the damaged endothelium, antigen-presenting cells (APCs), circulating antigen, and lymphocytes moving through the lymphatic system might reach the lymphatic tissue within the nodes. Additionally, the cortical layer contains rather large collections of rapidly dividing B-lymphocytes and helper T- lymphocytes in the peripheral lymph node. In the cortex, B cells predominate over T cells, despite the presence of both types of cells there. These lymphoid nodules are located near the follicular dendritic cells' (FDCs) branching, interlocking extensions. Depending on whether the nodule is a primary or secondary follicle, it may or may not have a germinal center.

The amount of antigen that lymph node cells are exposed to has a significant impact on the histological staining of lymph node samples. Furthermore, antigenic exposure affects the amount of cells in the node as well as the distinct separation of the cords. Because of this, the secondary follicle contains a diverse array of big B lymphocytes that have already been activated by stimulating antigens, whereas the primary follicle is made up entirely of tiny, dormant lymphocytes.[12][13]

Compared to secondary follicles, primary follicles absorb fewer histology stains. This is probably because the main follicle has fewer cells than the secondary follicle. Three further zones can be found within the germinal center: the mantle zone, the light zone, and the dark zone. Different components of B cell affinity maturation are facilitated by each zone. Quiescent B cells are located in the mantle zone, on the periphery of the germinal center. These cells have a heterochromatic nucleus, a small cytoplasmic volume, and strong basophilic staining. Additional cells seen in the mantle zone are macrophages and follicular dendritic cells, as well as the sporadic helper T lymphocyte. In the mantle zone, B cells might behave in two different ways. These cells either stay in the lymph node or develop into plasma cells that secrete antibodies while still being in the lymph node, or they change into memory B cells that re-enter the bloodstream.

The light zone and dark zone are the other two zones that make up the germinal center. Centrocytes that interact with follicular dendritic cells that display intact antigen on their surface are found in the light zone. Centrocytes that bind to the follicular dendritic cell antigen with high affinity will not die, whereas those that bind with low affinity will. While helper T cells maintain the remaining B cells and promote the class switching phase of cellular maturity, local macrophages assist in clearing out apoptotic B cells. The centroblasts in the dark zone of the germinal center are highly mitotic and highly likely to produce mutant antibodies.[14]

The paracortex

The paracortex lies deep within the cortical layer. Its edges merge with the deep medulla and superficial cortex. The main characteristics that set them apart were the lack of lymphoid nodules and the abundance of T lymphocytes in the paracortex's stroma, specifically both CD4+ and CD8+ T cells. Additionally, the paracortex has special venules called high endothelial venules (HEVs). These channels are used by the majority of lymphocytes that enter the lymph node. They consist of cuboidal endothelium with glycoproteins and integrins fitting apically. These two surface indicators permit lymphocytes to enter the lymph node from the percolating blood without obstruction (diapedesis). These specialized vessels can also be found in the lymphatic tissue associated with the mucosa, which is dispersed throughout the digestive system. Inside the lymph nodes, though, is where they are at their most developed.[12][13][14]

The medulla

The medulla is the lymph nodes innermost layer. The medullary cords and sinuses are the two additional regions into which it is separated both functionally and histologically. Along with B and T cells, plasma cells also occupy the cords. The cells are organized into centrally extended cord-like extensions from the paracortex. There is also an extensive network of reticular cell processes on the luminal surface of the sinuses. They function as the circulatory lymph's last line of defense.

The cortical sinuses, which are found in the periphery, terminate at the medullary sinuses.[12][13][14]

Eventually, they come together to create efferent lymphatic veins at the lymph nodes hilum. Squamous endothelium forms a single layer lining lymph vessels.

They have valves installed in them that facilitate the unidirectional passage of lymph from the lymph node to the efferent lymph vessels and back again from the afferent lymph vessels. The subcapsular area is filled with lymph that contains complement- bound or free-floating antigen thanks to the afferent lymph channels. Histology of lymph node illustrated in Figure (2.2).[12][13][14]

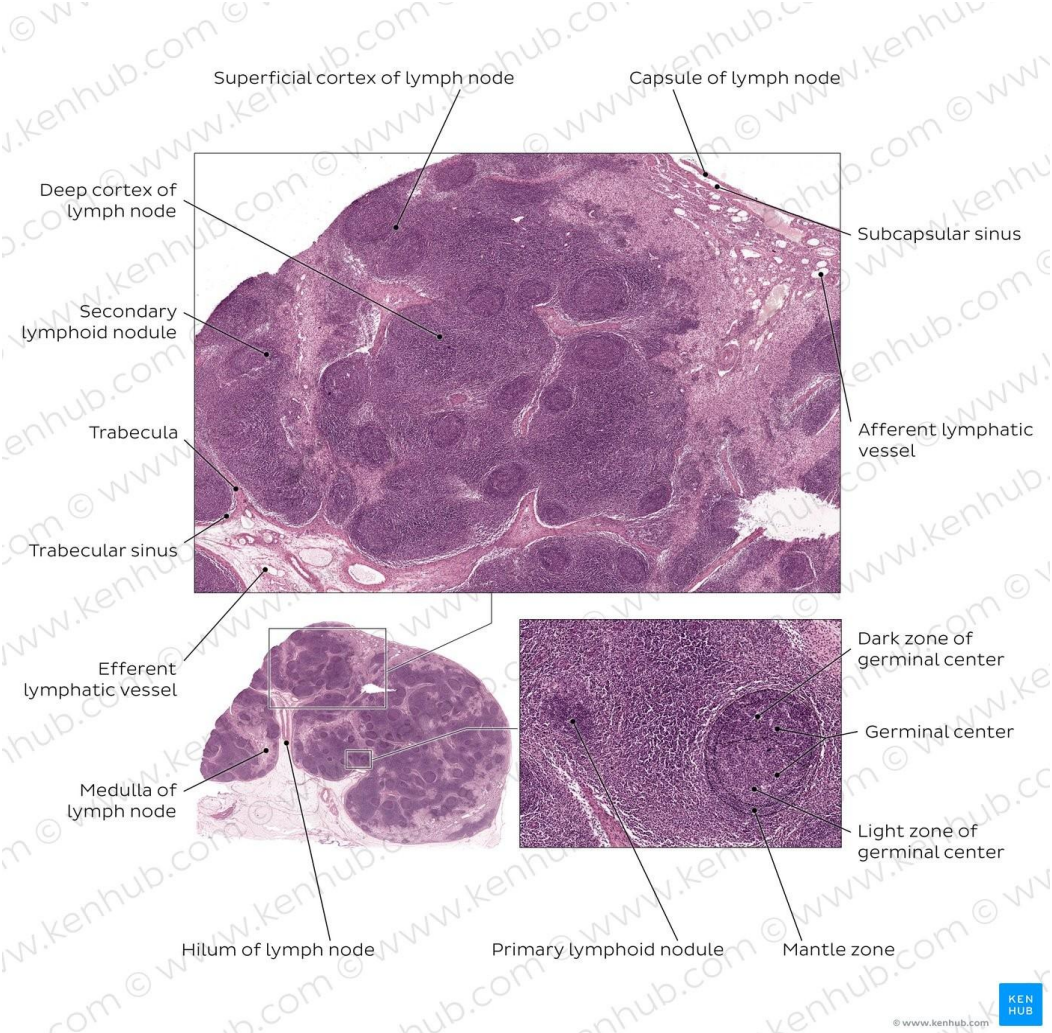

Figure 2:2. Lymph Node Histology.[13]

2.4. Definition of cervical lymphadenopathy

Lymphadenopathy is characterized by abnormally large lymph nodes or altered lymph node consistency or number.[1] When cervical nodal tissue has a diameter more than one centimeter, it is referred to be **cervical lymphadenopathy** (CLA).[2] Any size palpable supraclavicular node, however, is regarded as abnormal.[1] It's a symptom of an underlying pathology, not a disease in and of itself. It might be anything from a minor infection to a metastatic malignancy.[1]

2.5. Classification of cervical lymphadenopathy

2.5.1. Etiological classification

Based on its cause, cervical lymphadenopathy can be categorized as malignant, infectious, autoimmune, miscellaneous, or iatrogenic (medication-related). The acronym MIAMI makes these broad categories simple to recall.[1]

2.5.2. Pathological classification

Generally speaking, lymphoid hyperplasia or infiltration may be the pathological cause of cervical lymphadenopathy.[3]

1. Follicular hyperplasia, the most typical pattern of reactive lymphadenopathy is follicular hyperplasia. It is typically linked to sinus hyperplasia and/or paracortical hyperplasia in various degrees. It can affect people of all ages, even the very old, but it is most frequently observed in children and young adults. Clinically, the lymphadenopathy may be widespread but is typically confined. The most common affected sites are the cervical and axillary regions, which match the lymph node groups most prone to leak antigens.

In follicular hyperplasia, the lymph nodes sections histologically display hyperplastic follicles with enlarged germinal centers and paracortical areas; the follicles also show normal polarization; no major cytologic atypia is seen; and the staining pattern and distribution in the immunostains are normal.[15] The differences between follicular hyperplasia and lymphoma are shown in Table (2.1).

Table (2.1): Follicular Hyperplasia Versus Follicular Lymphoma.[15]

Follicular hyperplasia	Follicular Lymphoma
- Follicles limited to the subcortical region	- Follicles distributed throughout all nodal parenchyma
- Follicles don't extend beyond the capsule	- Extend beyond the capsule
- Follicles have variable sizes and shapes	- Similar size and shape
- Mixture of cell types in the population germinal centers	- Monomorphic or polymorphic
- Presence of tangible body macrophages	- Not present
- Distinct mantle zone	- Indistinct or absent
- Moderate to high mitotic rate	- low to moderate mitotic rate
- Preserved nodal architecture	- Contain areas of lost architecture
- Bcl-2 negative in B cells of germinal centers	- Bcl-2 positive in B cells of germinal centers
- No light chain restriction on immunostains (rare exceptions)	- Light chain restriction (20% in paraffin)
- No light chain restriction on flow cytometry	- light chain restriction when gated correctly (95%)
- Ig rearrangements absent	- Ig rearrangements usually detected (80%)
- Cytogenetic abnormalities infrequent, but have been described; t (14; 18) absent (rare exceptions).	- t(14;18)usually present 90%

2. In cases of malignant lymphoma or leukemia, as well as other cell types such as lipid cells and glycogen-laden macrophages, a lymph node may get infiltrated. The World Health Organization (WHO) has divided lymphoid and hematopoietic neoplasms into six categories: (1) precursor B and T cell neoplasm; (2) mature B cell neoplasm; (3) mature T cell and NK cell neoplasm; (4) Hodgkin's lymphoma; (5) histiocytic and dendritic neoplasm; and (6) post-transplantation lymphoproliferative disorders (LPDs).[3]

3. Spindle cell lesions of LN, including of (1) bacillary angiomatosis, (2) Kaposi sarcoma, (3) palisaded myofibroblastoma, and (4) inflammatory pseudotumor of LN, represent a new pathological entity.[5]

2.5.3. Clinical classification[16]

- Distribution-wise, cervical lymphadenopathy can be classified as localized (involving only one location), regional (involving two or more contagious areas), or part of a generalized (involving two or more noncontiguous areas).

- Duration: cervical lymphadenopathy is further divided into three categories: acute (duration: 2 weeks), subacute (duration: 2–6 weeks), and chronic (duration: does not resolve by 6 weeks).

2.6. Etiology of cervical lymphadenopathy

CLA can be caused by a variety of factors (Table 2.2). According to a recent cross- sectional study, the most likely cause of CLA varies depending on the age group: in individuals under the age of 14, reactive or nonspecific inflammation was the most common cause; in the group aged 14 to 59, tuberculous lymphadenopathy was the most common pathology; and in patients 60 years of age or older, cancer should be suspected.[7]

Table (2.2): Causes of cervical lymphadenopathy.[2][17]

Infectious	Infectious mononucleosis, Infectious hepatitis, Herpes simplex, Rubella, Measles, Adenovirus, HIV, Streptococcus, Staphylococcus, Cat-scratch disease, Tularemia, Tuberculosis, Syphilis, Leprosy, Diphtheria, Chlamydia, Lymphogranuloma venereum, Trachoma, Scrubtyphus, Rickettsial pox, Histoplasmosis, Coccidiomycosis, Toxoplasmosis, Leishmaniosis.
Malignanet	Hodgkin's lymphoma, Non-Hodgkin's lymphoma (NHL) ,Acute lymphoblastic leukemia ,Chronic lymphoblastic leukemia, Hairy cell leukemia, T cell lymphoma, Multiple myeloma with amyloidosis Metastasis.
Miscellaneous	Sarcoidosis, histiocytosis X, Kikuchi's disease, Kawasaki's disease, Castleman's disease Lymphomatoid granulomatosis
Medication	Allopurinol, Atenolol, Captopril, Carbamazepine, Cephalosporin, Gold, Hydralazine, Penicillin, Phenytoin, Primidone, Pyrimethamine, Quinidin
Immunological disease	Rheumatoid arthritis, systemic lupus erythematous (SLE), Sjogren's syndrome, drug hypersensitivity, Silicone associated Serum diseases, Graft versus host disease
Endocrine	Hyperthyroidism, Thyroiditis, Adrenal insufficiency

Lipid storage disorders	Gaucher's disease Niemann-Pick's disease

2.6.1. Infections

When an infectious agent localizes in the node itself or the draining nodes respond to an illness in the head and neck area, such as an upper respiratory infection, cervical lymphadenopathy may result.[9]

- Acute bacterial infections, the most common bacteria that cause acute bacterial infections are Staphylococcus aureus or Streptococcus pyogenes. Patients who have pustular or vesicular lesions of the face or scalp, a history of earache or discharge, or a history of sore throat or coughing that could indicate upper respiratory, skin, or ear infections, should be suspected of having an infection. Patients with periodontal disease or tooth abscesses may be suspected of having an infection with anaerobes such as bacteroides. Animal bites can result in Pasteurella multocida infection, while flea bites can result in Yersinia pestis illness.[18] In terms of clinical manifestation, adenopathy is typically unilateral, solitary, and affects the submandibular, upper deep cervical, submental, and occipital regions in decreasing order of incidence. The skin surrounding enlarged LNs is warm and erythematous, and the LNs themselves are painful and may fluctuate. The patient typically has a visible source of infection and has a fever.[3]

- Acute viral adenopathy usually occurs after an infection of the upper respiratory tract caused by an adenovirus, rhinovirus, parainfluenza virus, influenza virus, respiratory syncytial virus, and coronavirus. Herpes simplex, rubella, varicella, mumps, and measles are other less frequent etiologies. Clinically, bilateral and multifocal adenopathy is typical. The skin layer above the lymph nodes is neither warm nor erythematous, and the nodes themselves are often tiny, not sensitive, and rarely suppurate. In addition to a low grade fever, patients frequently report having a cough, rhinorrhea, conjunctivitis, or skin rash.[3]

Infectious mononucleosis

Is most frequent in children and adolescents and is brought on by the Epstein-Barr virus (EBV), which replicates inside B lymphocytes and pharyngeal epithelial cells and spreads mostly through saliva. Hoagland's criteria—at least 50% of lymphocytes and at least 10% of atypical lymphocytes in the event of fever, pharyngitis, and adenopathy—are used to make the diagnosis. The posterior group is typically affected by cervical adenopathy, which can also be linked to splenomegaly, inguinal adenopathy, or axillary adenopathy.[19] Together with reactive follicular hyperplasia, a notable proliferation of monocytoid B-cells may be the initial sign of acute infectious mononucleosis. But shortly after, there may be a noticeable immunoblastic growth. Usually, these cells have a lot of cytoplasm and noticeable nucleoli. They can imitate either non-Hodgkin lymphoma or Hodgkin lymphoma, have a high mitotic rate, form sheets, and be detected in sinuses. In addition to the often abundant plasma cells, eosinophils and epithelioid histiocytes may also be present. There may be a focal, widespread, or absent necrosis. Although reactive follicular hyperplasia is typically a prominent feature in follicles, paracortical hyperplasia sometimes overshadows this trait.[15]

- Chronic infectious lymphadenopathy, the hallmark of chronic infectious lymphadenopathy is the inability to get well after 2-4 weeks of the right kind of treatment.[19] In the pages that follow, significant causes of persistent infectious lymphadenopathy are discussed in detail.

Tuberculosis

The most typical extrapulmonary tuberculosis (TB) presentation in the world is tuberculous cervical lymphadenitis. To make the diagnosis, a tissue biopsy is often required for culture and histology. Fine needle aspiration (FNA), ultrasound-guided core lymph node biopsy, and excisional surgical biopsy are the diagnostic techniques that are currently accessible.[20] It is still one of the most common infectious diseases, especially in developing nations. Due to increased migration from developing nations and rising human immunodeficiency virus (HIV) incidence in these nations, industrialized nations face a health crisis brought on by tuberculosis.[21] Mycobacterium tuberculosis is the causal organism, while other mycobacteria may potentially be involved. Even though TB can affect almost any organ in the body, extrapulmonary affection most frequently affects the lymphatic system, with cervical lymph nodes being most frequently affected.[22] The affected nodal group is typically identified by the portal of entry; involvement of jugulodigastric LNs typically indicates an infection entering through the tonsils or adenoids, whereas supraclavicular lymphadenopathy typically indicates a pulmonary cause.[22] Tuberculous LNs exhibit caseation necrosis, epithelioid, macrophages, large cells, and sparse acid fast bacilli that appear as broken or beaded rods inside or outside of cells histopathologically.[23] A research including 102 patients with neck masses of tuberculous etiology revealed that 64%, 42%, and 18% of the patients experienced fever, weight loss, and sweating, respectively.[22] Jones and Campbell divided tuberculous lymphadenopathy into five phases on a local level as shown in (Table 2.3).

Table 2.3: Stages of TB lymphadenopathy.[24][25]

Stage	Description	Pathogenesis	Clinical features
1	Discrete LNs	Nonspecific reactive hyperplasia;	Large, firm and mobile LNs
2	Matted LNs	Periadenitis	Large and rubbery LNs, fixed to surrounding tissues
3	Cold abscess	Central softening and caseation deep to the deep fascia	Soft, smooth, nontender, fluctuant selling without involvement of the skin
4	Collar stud abscess	As a result of increased pressure caseous material perforate the deep fascia	Abscess is adherent to the overlying skin
5	Tuberculous sinus/ulcer	When the abscess bursts	Chronic nonhealing sinus or ulcer with thin, bluish, undermined edges and scanty watery discharge

Syphilis

Treponema pallidum, the bacterium that causes syphilis, can infect mucous membranes not just in the vaginal area but also in the head and neck, including the tonsils, lips, and tongue. Clinically, chancre is typically seen in the main infection site; its absence has been noted in a few cases when diagnosis becomes more challenging. Patients present as multiple, firm, mobile and non-tender enlarged lymph nodes. Histologic aspects that are characteristic include pericapsular chronic inflammation in conjunction with significant capsular fibrosis, follicular hyperplasia including a large number of plasma cells, endarteritis and phlebitis, and occasionally poorly formed granulomas. Certain Immunohistochemical stains, such as Warthin- Starry, are used to stain organisms; serology or PCR are used for confirmation.[26][27][28][29]

Cat-Scratch Disease

Cats can contract cat scratch sickness, a zoonotic illness brought on by Bartonella henselae. At least two of the following three requirements must be met for a diagnosis: (1) characteristic clinical signs present; (2) antibodies against B. henselae are detected serologically; and (3) Bartonella DNA is detected in the removed lymph nodes. Fever, lymphadenopathy, asthenia, pharyngitis, laryngitis, and skin rash are examples of clinical symptoms. The most prevalent clinical symptom is lymphadenopathy, with the cervical nodes being most commonly affected.[30] Necrotizing stellate abscesses encircled by palisading histiocytes are a hallmark of histology. Individuals may have involvement of one or more lymph node sites; upper extremity lymph nodes are more frequently involved, followed by cervical and inguinal lymph nodes.[31]

Toxoplasmosis

A zoonotic illness contracted by consuming raw meat that has Toxoplasma gondii oocytes from cat excrement. Ninety percent of cases have cervical lymphadenopathy, which may be accompanied by myalgias, fever, and sore throats.

Typically, the nodal enlargement is non tender, single, distinct, and movable.[32] The nodal architecture in Toxoplasma lymphadenitis remains intact. Clusters of epithelioid histiocytes, sheets of monocytoid B-cells with pale or clear cytoplasm, and hyperplastic lymphoid follicles with reactive germinal centers are the three primary histologic features in toxoplasma lymphadenitis. The lymph node sinuses have enlarged endothelial cells lining them. Membrane cords contain plasma cells and immunoblasts. Neither neutrophils nor eosinophils are present.[33]

2.6.2 Malignancy

Even though benign causes of CLA are more common, people with this condition can have an underlying malignant process. As a matter of fact, the primary goal when assessing CLA is to rule out cancer. Patients with CLA appear to have a significantly different rate of malignancy depending on their age, gender, and race. Malignant etiologies are more common as people age. In the age ranges of <14, 15–59, and ≥60 years, respectively, the rate of malignancy among patients with CLA was 12.1%, 21.7%, and 100%, according to a cross-sectional study by Biswas et al.[7] Shakya et al.[34], found that patients with CLA in the 51–60 year age range had a 50% malignancy rate in their study. Because the aforementioned age categories had such a high rate of malignancy, it was thought that any adult neck lump should be assumed of being malignant until proven otherwise.[35] Malignant cervical lymph nodes can arise from lymphoma or, less frequently, from secondary metastases from another primary.[7][17][34] Nonetheless, Magsi et al.,[36] discovered that lymphoma was more frequent than metastases in their audit of 140 CLA patients.

Naeimi et al.,[37] discovered that squamous cell carcinoma (SCC) was the most prevalent disease in the jugulodigastric group, irrespective of age, and that the larynx and hypopharynx were the most often detected locations for the initial tumor. Biswas et al.,[7] reported similar results, with adenocarcinoma ranking second in frequency. When it comes to the causes of malignant CLA, lymphoma comes in second most frequently, with NHL being more common in some series[7], while Hodgkin's lymphoma was more common in others.[37]

Clinical traits associated with CLA that point to a malignant enlargement includes[9]:

- Generally speaking, unlike Hodgkin's lymphoma, which causes the lymphadenopathy to be initially confined before spreading systematically to adjacent nodal regions, NHL typically manifests as generalized lymphadenopathy with or without hepatosplenomegaly. Systemic symptoms such as

pruritus, fever, weight loss, and sweats at night are referred to as B symptoms and are indicative of lymphoma, as they are less common in non-Hodgkin's type.

- Regionally: metastatic deposits from adjacent melanoma or papillary thyroid carcinoma may be indicated by a pigmented cutaneous lesion or mass that is movable upon deglutition.
- Locally, the largest risk of cancer is associated with enlarged supraclavicular LN, which is usually a cause for concern.

While rubbery or firm mobile nodes are more suggestive of lymphoma, amalgamation and limiting of mobility may occur later, hard, fixed, painless lymph nodes are strongly suggestive of metastatic deposits.

Hodgkin Lymphoma

Hodgkin lymphoma (HL) is typified by malignant Reed-Sternberg cells within an inflammatory background. Patients with supra-diaphragmatic lymphadenopathy who come with systemic B symptoms are typically diagnosed in their 20s and 30s. Typically, the cancer cells make up a small portion of the tumor and are encircled by an inflammatory background that is reactive and made up of histiocytes, lymphocytes, eosinophils, neutrophils, and plasma cells. Hodgkin and Reed-Sternberg (HRS) cells are the collective term for these malignant cells, which can be either big mononuclear cells or pathognomonic multinucleate giant cells.

Based on appearance and immunohistochemistry, Hodgkin lymphoma is classified as either nodular lymphocyte predominate (NLPHL) or classical Hodgkin lymphoma (cHL). With over 90% of cases being cHL, which acts like an aggressive neoplasm, NLPHL typically has a slow-growing biology.

The histologic subgroups of classical Hodgkin lymphoma are distinguished by background infiltration and HRS cell abundance. All cHL subtypes have malignant HRS cells that have the distinct immunophenotypic pattern of CD15 +, CD30 +, and CD45−. Classical Hodgkin lymphoma involves cervical > axillary, mediastinal, and paraaortic lymph nodes.[38][39]

- **Nodular sclerosis classical Hodgkin lymphoma** is the most prevalent subtype of cHL, makes up roughly 70% of cases in the industrialized world.

It is distinguished by neoplastic lacunar type HRS cells within an inflammatory context of band-forming sclerosis. About half of the patients have bulky nodes (>10 cm in diameter), and 80% of cases have mediastinal adenopathy. There is a lower frequency of association with the Epstein-Barr virus (10 - 25%), and nodular sclerosis subtype has a generally better prognosis than other forms of CDH. Typical sites of involvement in nodular sclerosis are mediastinal, cervical, supraclavicular lymph nodes.[38][39]

- **Mixed cellularity classical Hodgkin lymphoma**, although it makes up 20–25% of cHL in the United States, people with HIV infection and those living in developing nations are more likely to have it. There is no sclerosing fibrosis and the HRS cells are dispersed in a diffuse mixed inflammatory background. Compared to nodular sclerosing cHL, the expression of Epstein-Barr virus encoded latent membrane protein 1 (LMP1) and EBV encoded small RNA (EBER) is significantly more common (about 75% of cases). Typical sites of involvement are peripheral lymph nodes, spleen, and bone marrow.[38][39]

- **Lymphocyte rich classical Hodgkin lymphoma,** makes about 5% of cases of classical Hodgkin lymphoma (cHL), specimens feature a nodule or diffuse cellular background of small lymphocytes with sporadic HRS cells without neutrophils or eosinophils. Patients typically present with early stage illness and likely to have peripheral adenopathy without substantial mediastinal involvement.

Excellent treatment results are achieved. This subtype of classic Hodgkin lymphoma has 40% association with EBV.[38][39]

- **Lymphocyte depleted classical Hodgkin lymphoma,** is the least common cHL subtype in affluent countries, making up less than 1% of cases. HRS cells have a diffuse infiltrate into tumor specimens; there is no discernible reactive inflammatory infiltrate. Compared to the other cHL subtypes, it has a more severe clinical course and is frequently observed in conjunction with HIV infection. Typical sites of involvement are retroperitoneal lymph nodes, abdomen, and bone marrow. More than 90% of cases show positive infection of RS cells with EBV.[38][39]

- **Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)** is a B cell neoplasm with excellent prognosis and no association with EBV, it makes up to 5–10% of cases of Hodgkin lymphoma, characterized by sporadic clonal cells, lymphocyte predominant cells, against a background of reactive lymphocytes and histiocytes. The development pattern of NLPHL cells is primarily nodular but can also be diffuse. Unlike classical Hodgkin lymphoma, CD30 is variably positive and if positive, is usually weak and most cases are negative for CD15, typical site of involvement is peripheral lymph nodes, generally cervical, axillary, and inguinal.[38][39]

Non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL), is tumor of the lymphoid organs, develops from B cell progenitors, mature B cells, T cell precursors, and mature T cells.

Follicular lymphoma (approximately 20%) and diffuse large B-cell lymphoma (about 30%) are by far the most prevalent NHL subtypes in developed nations. The frequency of the remaining NHL subtypes is less than 10%. In the USA, NHL is the sixth most common cause of mortality from cancer. These cancers' natural histories differ greatly from one another. When left untreated, aggressive lymphomas can cause deaths in a matter of weeks due to particular B symptoms such weight loss, fever, and night sweats. In contrast, indolent lymphomas typically appear with waxing and waning lymphadenopathy over many years.[40][41]

Follicular lymphoma, splenic marginal zone lymphoma, and chronic lymphocytic leukemia/small lymphocytic lymphoma are examples of lymphomas that typically show in an indolent manner. Diffuse large B cell lymphoma, Burkitt lymphoma, adult T cell leukemia/lymphoma, precursor B and T cell lymphoblastic leukemia/lymphoma, and a few other peripheral T cell lymphomas are examples of aggressive lymphomas. Peripheral lymphadenopathy may be seen in up to two thirds of patients. Ten to thirty-five percent of patients have primary extranodal lymphoma upon diagnosis, and the remaining patients develop extranodal disease (secondary extranodal disease) during the course of their illness. The most common head and neck presentation in NHL is cervical lymphadenopathy, which is characterized by many painless nodes. These lesions are not attached to the deep planes or the skin, and they are not as hard as metastatic nodules. NHL more frequently spreads to nodes that are not adjacent. Abdominal involvement is more common than mediastinal involvement.[40][41]

- **Follicular lymphoma,** Mature B cell neoplasm, also known as biologically indolent lymphoma, is a malignancy of germinal center B cells (centrocytes and centroblasts). 80% of all follicular lymphomas are systemic nodal tumors, Cervical and inguinal lymph nodes are more frequently affected. Anomalies in genetics the basic mechanism is a translocation t (14; 18), which involves rearranging the bcl-2 gene. Regarding morphology, Follicle lymphoma cells are the same as those found in a normal germinal center. Centrocytes: less than twice the size of tiny lymphocytes; cytoplasm is pale and sparse; nuclei seem sliced and irregular; there may be one or more nucleoli present.[40][41]

Centroblasts are 3–4 times larger than tiny lymphocytes; they include 1-3 basophilic nucleoli opposed to the nuclear membrane, a narrow ring of cytoplasm, and round or oval nuclei.[40][41]

- **Diffuse large B cell lymphoma (DLBCL),** is most prevalent adult non-Hodgkin lymphoma (~30%), occurs across all age groups, and has a slight male predominance. The median age at diagnosis is the seventh decade. Lymph nodes are the usual site of involvement, with ≥ 1 extranodal involvement site in 71% of cases, and completely extranodal involvement in 40% of cases. Under a microscope, it is distinguished by a diffuse infiltrate of large (or occasionally medium-sized) aberrant B lymphoid cells with vesicular chromatin and conspicuous nucleoli that partially or completely effaces normal tissue architecture. Morphological variants of DLBCL are:

- Immunoblast: solitary central nucleolus
-Centroblastic: two to four nucleoli
-Anaplastic variant: anaplastic nuclei, which can resemble Reed-Sternberg cells or anaplastic large cell lymphoma.[40][41]

Metastasis

Most squamous cell carcinomas (SCC) that metastasize to the cervical lymph nodes are formed from initial tumors that are situated on the mucosa. Even though the main tumor is typically visible at first presentation, this isn't always the case. Metastatic SCC in the oro-pharynx, most commonly the base of the tongue and the pharyngeal tonsils, is usually accompanied with sub-clinical disease in the absence of apparent clinical or radiological symptoms of a head and neck primary.[42] Oral cancer typically progresses by direct invasion into the mandible, base of the tongue, anterior tonsillar pillar, and floor of the mouth. At the time of presentation, metastases from cervical lymph nodes occur in between 30% and 40% of patients. There exists a direct correlation between the thickness and T stage of the tongue lesion and the likelihood of lymph node involvement. Most often, the subdigastric nodes are affected. Less frequently affected lymph nodes are the submandibular and midjugular ones; posterior cervical, lower jugular, and submental nodes are seldom affected. The most common initial symptom and indicator of nasopharyngeal cancer is a neck lump. Usually, near the tip of the mastoid, a mass is felt beneath the superior side of the sternocleidomastoid muscle and visible in the upper posterior neck. About 50% of cases have bilateral cervical lymph node metastases. The Para pharyngeal, jugulodigastric, and upper posterior cervical nodes are the most commonly affected nodes. The next most frequently implicated nodes are the midjugular and midposterior cervical, then the lower jugular and supraclavicular nodes. Occasional involvement of the occipital and submental nodes occurs, usually in the context of extensive cervical lymphadenopathy in the more frequently implicated neck sites. Patients with metastatic preauricular nodes only infrequently present.[43]

When a lymph node biopsy reveals identifiable glandular components, metastatic adenocarcinoma is diagnosed. The mucosal sero-mucinous glands or the major salivary glands (parotid, submandibular, and sublingual glands) are the primary sources of salivary gland-type adenocarcinomas found in the head and neck region.[42] When the core biopsy often contains sheets of malignant

cells without any morphological information to direct the immunohistochemistry investigation in cases of malignant cervical lymphadenopathy, Staged panels of tests are the most effective way to handle these patients. A basic panel is made to classify the malignancy into one of four main categories: sarcoma, lymphoma, carcinoma, and melanoma.[42]

The most prevalent kind of thyroid cancer is papillary thyroid carcinoma (PTC), which typically manifests as a lump in the neck or cervical node or as a painless thyroid nodule, 67% in the thyroid alone at presentation, 13% in the thyroid plus cervical nodes, and 20% in the nodes alone. Because nodes are tiny and have comparable consistency, nodal involvement is frequently not clinically evident. Medullary thyroid carcinoma in up to 75% of patients has nodal metastasis, mostly involving central compartment, ipsilateral and contralateral jugulocarotid chains. Follicular thyroid carcinoma in less than 5% has ipsilateral cervical lymphadenopathy.[44]

About 5–10% of all cancers are carcinomas of unknown primary, which are malignancies that appear with lung metastases while attempts to determine the source site of the malignancy are unsuccessful. SCC is the most prevalent histological type, followed by adenocarcinoma, undifferentiated malignancy, and other rare histological types like melanoma and lymphoma. A good percentage of CUP patients present with cervical nodal metastases. Level II LNs are most frequently affected, followed by level III LNs, and such affection is usually unilateral.[9]

While isolated lower neck LN affections are typically linked to malignancies below the clavicles, higher and middle neck LN affections are typically related to the head and neck region. The head and neck region accounts for over 25% of pediatric cancer cases, with the cervical nodes being the most common location.[9]

During the first six years of life, neuroblastoma and leukemia are the most common cancers linked to cervical nodes, followed by NHL and rhabdomyosarcoma. Six years later, the most common cancer is Hodgkin's lymphoma (HL), which is followed by rhabdomyosarcoma and NHL.[9]

2.6.3. Endocrine Disease

More than 80% of patients with autoimmune thyroiditis (AIT) showed cervical lymphadenopathy (levels II–IV, VI), according to Sahlmann et al.[45] Similarly, in 23% of cases of Hashimoto's thyroiditis (HT), cervical lymphadenopathy was found.[46] Cervical lymphadenopathy has also been shown to be related with Graves' disease.[47] Reactive lymphoid hyperplasia is the pathology. Consequently, while making a differential diagnosis for individuals with thyroid nodes and cervical LNs, AIT, including HT, should be considered. When a patient exhibits clinical signs of chronic adrenal insufficiency and has cervical lymphadenopathy, the doctor should be made aware of the extremely rare primary adrenal lymphoma or the likelihood of secondary adrenal involvement.[48][49]

2.6.4 Autoimmune Disease

Lymphadenopathy can be observed as a physical finding in nearly all cases of autoimmune disorders, but it is particularly common in 82% and 69% of cases of RA and systemic lupus erythematous (SLE), respectively. Cervical node adenopathy is the second most common type of these illnesses, behind axillary lymphadenopathy.[50]

To distinguish it from lymphoma, which has an interfollicular area with numerous mitoses, few plasma cells, and compressed reticulin fibers, inflamed nodes histopathologically display reactive follicular hyperplasia, polyclonal plasma cell infiltration with sporadic mitosis, moderate vascular proliferation, and no compression of reticulin fibers.[50]

When it occurs, axillary and/or inguinal lymphadenopathy is frequently linked to cervical lymphadenopathy. The majority of lymph nodes are numerous, comparatively little, pliable, soft, and non-tender.[51] The basis for the diagnosis should be the pertinent laboratory and clinical criteria. Acute phase reactants (APR), anti-citrullinated protein antibody (ACPA), and serum rheumatoid factor increase, along with polyarthritis of small joints lasting longer than six weeks, are diagnostic indicators for Reumatoid arthritis.[52]

SLE is diagnosed by the presence of increased antinuclear and anti-DNA antibodies, as well as malar and discoid rashes, nonerosive arthritis, photosensitivity, mouth ulcers, and renal, neurologic, and hematologic problems. Sjogren's syndrome may be suggested by dry mouth and eyes. Cervical lymphadenopathy is present in most SLE patients. Microscopically, lymph nosed in SLE show preservation of the architecture but hyperplasia of the follicles with varying sizes, enhanced vascularity, interfollicular immunoblasts, and plasma cells. Paracortical necrosis frequently occurs in well-defined regions, affecting tiny arteries.[53]

2.6.5. Drug-Induced Lymphadenopathy

Diffuse lymphadenopathy can be caused by some drugs, the most well-documented of which being phenytoin-induced lymphadenopathy in the literature. The reaction normally appears a few months after therapy starts and goes away a few weeks after the medication is stopped. Pathology typically reveals polymorphous infiltration of lymphocytes, plasma cells, and eosinophils that partially or completely obscure the architecture of the lymph nodes.[54][55]

In instance, phenytoin has also been linked to pseudolymphoma, a nodal pathology that is distinctive. Lack of T cell clonal growth is the basis for differentiation from lymphoma. In terms of clinical manifestation, bilateral cervical adenopathy is typically a component of generalized lymphadenopathy. The illness

is frequently accompanied by eosinophilia, rash, and fever. Since lymphoma and this condition might readily be confused, a high index of suspicion should be maintained at all times. The proper diagnosis can be determined by looking at the patient's medical history, improvement after stopping phenytoin, and the pathological examination of a surgically removed lymph node.[54][55]

2.6.6. Miscellaneous Causes of Cervical Lymphadenopathy

Kawasaki Disease (KD), it is also referred to as lymphocutaneous illness and is a form of systemic vasculitis with an unclear origin. It usually affects kids younger than five years old. Between 42% and 65% of KD patients had cervical lymphadenopathy. Adenopathy is histopathologically caused by swelling of the paracortical zone and growth of the sinus.[56][57]

Additionally, necrotic foci that grow beneath the capsule and are accompanied by fibrin thrombi in the nearby tiny arteries can indicate ischemia alterations in lymph nodes. Clinical suspicion should be made for the following conditions before making a diagnosis: (1) fever lasting longer than five days; (2) unilateral cervical lymphadenopathy; (3) edema, erythema, and/or desquamation of the palms and soles; (4) non-purulent bilateral conjunctivitis; and (5) strawberry tongue.

Since 25% of untreated children have coronary artery anomalies (aneurysm, thrombosis, or infarctions) that aggravate their condition, a high index of suspicion should be maintained when evaluating these children.[56][57]

Sarcoidosis, it is an inflammatory chronic multisystem illness with an unclear cause. Though it only makes up 1.7% of all cases of head and neck lymphadenopathy, cervical lymphadenopathy is the most prevalent manifestation of the illness in this region. It is distinguished histopathologically by noncaseating epithelioid cell granulomas. The diagnosis of hilar lymphadenopathy, pulmonary infiltration, and cutaneous and eye lesions is typically made based on congruent clinical and radiologic findings. But when the only clinical symptom is isolated cervical lymphadenopathy, a diagnostic conundrum occurs.[58][59]

Langerhans cells histiocytosis, It's an uncommon illness that mostly affects kids. Reactive versus neoplastic genesis is a contentious issue. Nodal involvement can occur as a single lesion or, more frequently, as a component of a systemic illness.[61] The presence of clonal proliferation of antigen-presenting dendritic cells known as Langerhans cells (LCs) is the pathogenic hallmark, which is also referred to as Langerhans cells histiocytosis.[59][60]

The disease's clinical severity ranges widely. The most common kind, known as eosinophilic granuloma, is characterized by isolated lesions in the stomach, lungs, skin, or bones. The trio of exophthalmos, lytic bone lesions, and diabetes insipidus describe the disease's moderate form, known as Hands-Schuller-Christian disease. The most severe kind, a multisystem condition that poses a risk to life, is called Letterer-Siwe disease. Fine-needle aspiration cytology, which shows many LCs through their distinctive nuclear features, such as nuclear grooves and pseudoinclusions, and immunohistochemical detection of positivity for S-100, peanut agglutinin, MHC class II, CD1a, and langerin (CD207) can both be used to make the diagnosis.[59][60]

Kikuchi-Fujimoto Disease, This condition, which primarily affects young Japanese women, is benign and self-limiting. Although the etiology is uncertain, an infectious cause has been suggested. The lymph node (LN) exhibits histiocytic necrotizing lymphadenitis, which is defined as a single or several regions of necrosis with histiocytic cellular infiltration. Clinically, leucopenia, fever, and regional lymphadenopathy are the most common presentation symptoms. The illness may manifest in the context of SLE and be linked to autoimmune manifestations.[61]

Castleman's Disease, It is an etiologically unknown lymphoproliferative disease (LPD). On a histopathological level, LNs exhibit endothelial hyperplasia, significant capillary proliferation, and follicular hyperplasia. The hyaline vascular type and the plasma cell type are the two pathological types that have been identified. There are two variations in terms of therapy: multicentric and unicentric. In the unicentric variety, the disease is typically unintentionally identified on imaging,[62][63] which typically identifies mediastinal or hilar lymphadenopathy. The patient is frequently asymptomatic. The multicentric form is a systemic illness that typically manifests as hepatosplenomegaly, severe peripheral lymphadenopathy, and recurrent fevers, sweats, and exhaustion. Clinical suspicion, histological analysis, and immunohistochemical identification of elevated vascular endothelial growth factor expression are the three main diagnostic criteria.[62][63]

2.7. Clinical features of abnormal lymph node enlargement

The most prevalent causes of abnormal lymph node enlargement include infection/immune response, malignancy, and, less frequently, macrophage infiltration containing metabolite deposits (e.g., storage disorders). The lymph nodes that are infected usually feel warm, swollen, sensitive, and firm. It is possible for inflammation to migrate to the skin on top of it and make it look red. Malignant lymph nodes are often hard, non-tender, matted, fixed, and they tend to get bigger over time. Nodes up to 1 cm in diameter are usually regarded as normal; however, some writers propose that nodes bigger than 1.5 cm in the inguinal region or greater than 0.5 cm in the epitrochlear region should be regarded as abnormal.[64]

Children's granulomatous disorders (such as tuberculosis, cat-scratch disease, or Sarcoidois) or cancer (mostly lymphomas) were predicted by lymph nodes larger than 2 cm in diameter, an abnormal chest radiograph, and the absence of symptoms related to the ears, nose, or throat. Nodal size increases significantly on serial examinations. Therefore, nodes that exhibit continuous growth are significant, whereas those that exhibit regressive growth tend to be more comforting.[64]

When a lymph node grows rapidly, its capsule expands and produces pain. Inflammation or purpuration are the primary causes of pain, however bleeding into the necrotic core of a malignant node can also cause pain. Hard, stony nodes are frequently indicative of metastatic malignancy. Rubbery, extremely hard nodes may indicate lymphoma. Infections or inflammatory diseases produce softer nodes. Nodes with suppuration may fluctuate. "Matted" nodes are those that appear to move as a cohesive unit and have a sense of connectivity. Matte nodes can be malignant (such as lymphomas or metastatic cancer) or benign (such as TB, sarcoidosis, or lymphogranuloma venereum).[64]

Fever, weight loss, exhaustion, and night sweats are examples of constitutional symptoms that may indicate conditions including lymphoma, TB, collagen vascular diseases, infection, or cancer.[64]

2.8. Risk factors for malignancy in lymphadenopathy

These are the recommendations for prompt biopsy referral in order to rule out cancer.
- Age over forty years old.
LAP duration longer than 4-6 weeks-
-generalized LAP.
-Male sex
-Supraclavicular lymph nodes.
-Nodes not returned to baseline levels within 8–12 weeks.
-The lymph nodes are hard, firm, and non-tender; they measure more than 2 cm or are gradually growing larger.[65]
-When there is no dermatitis or local infection, axillary nodes are affected.-Systemic symptoms include hepatosplenomegaly, fever, sweats at night, and weight loss.
-Race: White.[65]

2.9. Diagnosis of cervical lymphadenopathy

One helpful imaging technique for evaluating cervical lymph nodes is ultrasound. The echogenic hilum's size, shape, and condition as well as the development of micro nodules, intranodal necrosis, and calcification are all useful characteristics. When identifying tuberculosis, adjacent soft tissue edema and matting are especially helpful. It can be used in conjunction with fine-needle aspiration cytology.

When paired with fine-needle aspiration cytology, ultrasound's excellent sensitivity (98%) and specificity (95%) make it a valuable imaging tool for evaluating cervical lymphadenopathy. A short-axis diameter of 5 mm or more can be used to identify the existence of enlarged cervical lymph nodes using computed tomography imaging. Excisional biopsy is still the preferred diagnostic method. In order to prevent cancer cells from an undetected cervical metastasis from contaminating the neck, lymph nodes should ideally be fully removed rather than incised. A biopsy of this kind may result in seromas, hemorrhage, infection, and lymph leakage, among other problems.[64]

Fine needle aspiration (FNA): has advantages than open biopsy, it is simpler, and leaves no scar to interfere with future surgical procedures, and do not require a wait between diagnosis and treatment. If a peroperative positive histological diagnosis is made, an open biopsy may be performed if a frozen section and concurrent definitive neck dissection can be performed in the event that a needle biopsy is unable to make a cancer diagnosis.[66]

It has been stated that a pathologist should only attempt a diagnosis of FNA if they are fully aware of the specifics of the patient's medical history, physical examination, and other laboratory test results. These will make up for the FNAs shortcomings in showing the tissues' architectural layout more so than histology sections. When interpreting FNA, clinical data provides a safety net, and pathologists shouldn't be prejudiced. Because they are easily accessible, lesions in the head and neck area are especially well-suited for FNA diagnosis. The most advantageous aspect of needle biopsy for patient care is how quickly the results are obtained, allowing for the planning of early diagnosis and subsequent treatment within a few hours of the consultation. Furthermore, FNA is affordable, accurate, and simple to use.[66]

Biopsy

In cases of persistent CLA with a high estimated risk of malignancy and widespread lymphadenopathy for which the first workup is non-diagnostic, a biopsy is necessary.

Excisional biopsy: to differentiate between Hodgkin's and non-Hodgkin's lymphoma, an excisional biopsy is necessary for diagnosis. It needs to be extracted from the largest or most atypical LN location. If there is a high estimated risk of malignancy, a biopsy that yields no results should be regarded as non-diagnostic rather than negative and additional investigation is necessary. Atypical lymphoid hyperplasia found in the biopsy results should once more be regarded as non- diagnostic, and additional workup, including a second biopsy, should be taken into consideration.[9]

When imaging or serological assays are unable to show that LNs are reactive due to a bacterial or viral etiology, tissue biopsy of LNs remains the standard criterion.[9]

Core needle biopsy: using automated needles for a

Ultrasound (US) guided core needle biopsy results in a higher yield of tissue sample, a specimen with maintained histological architecture that permits the use of several histological and immunohistochemical procedures, and a more accurate diagnosis. Additionally, a core needle biopsy may be sufficient to diagnose lymphoma without the requirement for an additional excisional biopsy. A study involving 247 patients with cervicofacial lymphadenopathy demonstrated that US guided core needle biopsy could distinguish between benign and malignant lymph nodes with a 100% specificity, 98.7% sensitivity, and accuracy. Eighty percent of lymphoma cases in the same study may be treated without requiring an excisional biopsy.[9][67]

The likely harm to nerves or the vessels components (which can be mitigated with imaging guided biopsy) and tumor cell spilling (needle-track metastases) are the conventional drawbacks. Nonetheless, following the application of cutting needle biopsies in head and neck tumors in a large series, Southam et al., did not discover any instances of track metastasis throughout a 7-year follow-up period.[68]

When FNAC results are unclear and a high index of suspicion exists, it makes sense to perform a core needle biopsy. This is especially true when excisional biopsy is either impractical given the patient's overall health or is not possible because the nodal tissue has attached itself to nearby structures.[9][68]

3.1. Study design

A retrospective analysis of 160 randomly chosen patients with cervical lymphadenopathy who were gathered from the Teaching Laboratory of Al-Imamain Al-Kadhimain Medical City, the Pathology Departments of Ghazi Al-Hariri Surgical Specialties Teaching Hospital, and Teaching laboratories of medical city between January 2024 and December 2024, the samples were collected between January 2018 and December 2023.

The slides and histopathology reports for each case were revised, reexamined, and studied in retrospect. The pathology reports of the patients were also used to extract the clinical parameters, which included age, sex, related clinical features, duration, site, gross finding including: size, single or multiple lymph nodes discrete or matted lymph nodes and consistency, neoplastic and non-neoplastic diagnosis, primary vs. secondary neoplasm, and histopathological subtypes of primary and metastatic tumors.

The practical work of this study includes

1. Gathering 160 slides and histopathology reports from the lymph node sample.
2. The study's supervising pathologist examined and reassessed Hematoxylin and Eosin (H&E) stained slides in the Pathology Department at College of Medicine/Al- Nahrain University in order to revise the histological diagnosis.

3.2. Ethical consideration

The scientific committee of the Iraqi Board of Medical Specializtion approved the study (approval number: path 3, approval date; 21st February 2024).

3.3. Inclusion and exclusion criteria

Inclusion criteria

Patients with cervical lymphadenopathy.

Exclusion criteria

Samples with insufficient patient data.

3.4. The statistical analysis

Version 26 of the Statistical Package for Social Sciences (IBM SPSS) software was used for all statistical analyses. Mean SD was used to express continuous variables. When appropriate, the Chi-square test was used to compare groups and evaluate the proportions of nominal and ordinal variables in each group. Statistical significance was defined as a P value of less than 0.05.

4.1. The study sample

A total number of 160 patients were included in this study.

4.2. Age and sex of the study sample

The distribution of age among the studied patients shows that the most common age group is <20 year followed by >50 years and the mean age for the patients was 31 year. As shown in **(Table 4.1)**. Male patients were slightly more than females with M: F ratio = 1.46:1 as shown in (**Figure 4.1).**

Table (4.1): Distribution of age groups among the studied patients.

Age category	Frequency	Percentage %
<20	44	27.5
20-29	31	19.38
30-39	22	13.75
40-50	20	12.5
>50	43	26.87

Total	160	100 %

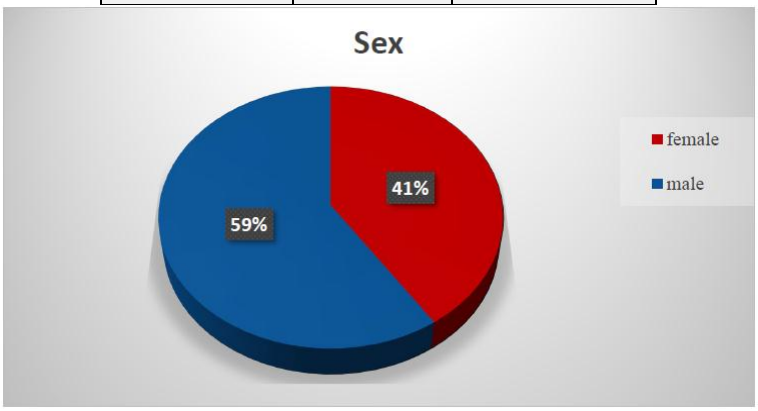

Figure (4.1): Distribution of sex among the studied patients.

4.3. The clinical presentation of patients

The most common clinical presentation was LAP accompanied by other symptoms (fever, weight loss, night sweats) 43.8%, followed by tender LAP 36.9%, then LAP with history of secondary neoplasm 19.3% as shown in (**Table 4.2).** About 78.7% had chronic duration compared to 21.25% had acute duration as shown in **(Figure 4.2)**.

Table (4.2): Clinical presentation of patients.

Clinical presentation	Frequency	Percentage %
Tender LAP	59	36.9
LAP and other symptoms (fever, weight loss, night sweats)	70	43.8
LAP with history of secondary neoplasm	31	19.3
Total	**160**	**100%**

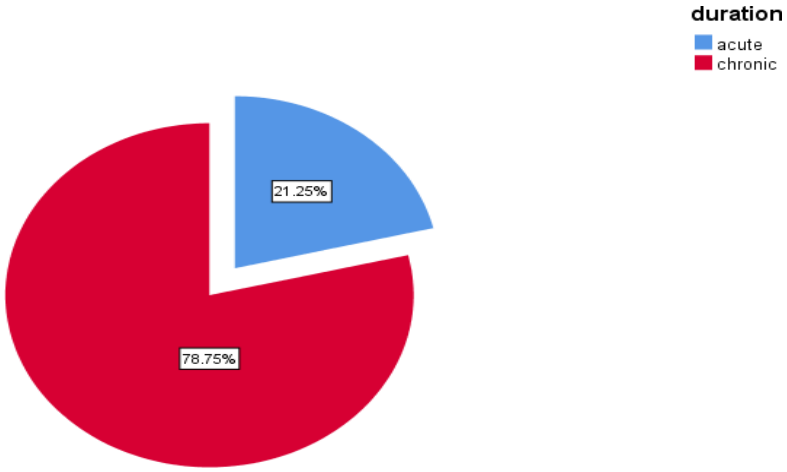

Figure (4.2): Duration of lymph node enlargement.

4.4. Level of lymph nodes involvement

Level IV (lower jugular group), had the highest frequency of lymphadenopathy in this study (22.5%), followed by Level III (the middle jugular group) (21.9%), Level II (upper jugular group) (18.8%), and Level V (posterior triangle group) (13.8%) as shown in **(Table 4.3).**

Table (4.3): Level of lymph nodes involvement.

Level	Frequency	Percentage %
I	16	10.0
II	30	18.8
III	35	21.9
1V	36	22.5
V	22	13.8
VI	8	5.0
Multiple levels	13	8.0

Total	160	100%

4.5. Size, number and gross feature of lymph nodes in the study sample

Shows that 66.2% of the enlarged nodes were 2-5 cm in size and 30% were < 2cm in diameter. And only 6 out of 160 cases were larger than 5 cm as shown in (**Table 4.4).**

Table (4.4): Size of enlarged lymph nodes.

Lymph node size in cm	Frequency	Percentage %
<2	48	30.0
2-5	106	66.25
>5	6	3.75
Total	**160**	**100 %**

About 59.4% LAP cases had multiple enlarged nodes as shown in **(Table 4.5)**. About 53.68% were discrete grossly as shown in **(Figure 4.3)**, 62.5% had firm consistency as shown in **(Figure 4.4).**

Table (4.5): Number of enlarged lymph nodes.

No. of enlarged nodes	Frequency	Percentage%
Multiple	95	59.4
Single	65	40.6
Total	160	100.0

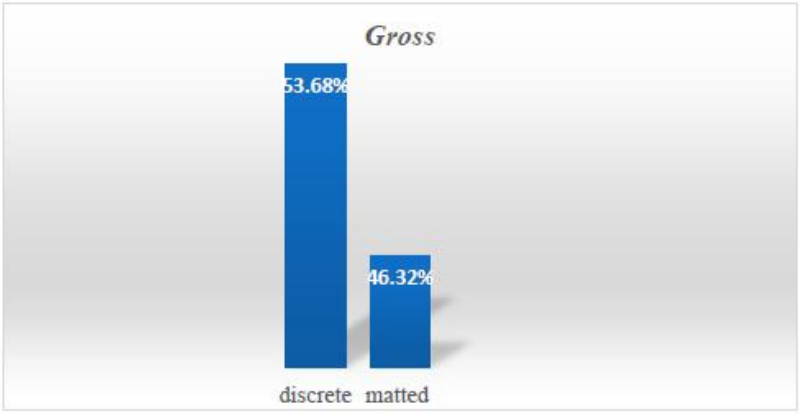

Figure (4.3): Gross appearance of lymph nodes.

Figure (4.4): Consistency of lymph nodes.

4.6. Histopathological diagnosis of the studied sample

The most frequent cause of cervical LAP in this study was reactive lymphadenopathy (35%), which was followed by tuberculosis (17.5%), metastases (17.5%), Hodgkin lymphoma (15%) and non-Hodgkin lymphoma (11.9%) as shown in (**Table 4.6**). And generally, non neoplastic causes were more common than neoplastic causes as shown in **(Figure 4.5).**

Table (4.6): The final diagnosis among the examined lymph nodes.

Diagnosis	Frequency	Percentage %
Reactive lymphadenopathy	**56**	**35.0%**
Tuberculosis	**28**	**17.5%**

Toxoplasmosis	**5**	**3.12%**
Hodgkin lymphoma	**24**	**15.0%**
Non-Hodgkin lymphoma	**19**	**11.9%**
Metastasis	**28**	**17.5%**
Total	**160**	**100%**

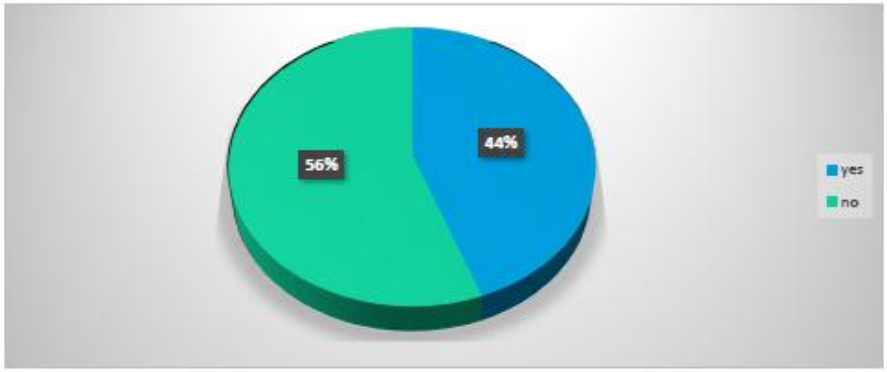

Figure (4.5): The cause of the enlarged lymph node (yes= neoplastic cause) (no= non neoplastic).

4.6.A. Distribution of benign diseases: Out of 160 cases, 89 cases were benign, the most common diagnosis was follicular hyperplasia followed by tuberculosis as shown in **(Table 4.7).**

Table (4.7): Distribution of benign diseases.

Benign diagnosis	Frequency	Percentage %
Follicular hyperplasia	**53**	**59.55%**
Tuberculosis	**28**	**31.46%**
Toxoplasmosis	**5**	**5.62%**
Reactive sinus hyperplasia	**1**	**1.12%**
Rosai Dorfman disease	**1**	**1.12%**
Langerhans cell histiocytosis	**1**	**1.12%**
Total	**89**	**100%**

4.6.B. Subtypes of Hodgkin lymphoma: Out of 160 cases, 24 cases were diagnosed as Hodgkin lymphoma; 23 cases of them were classic Hodgkin lymphoma and 1 case was NLPHL. The most common subtype of classic HL is mixed cellularity (45.83%) followed by nodular sclerosis (37.5%) and lymphocyte rich type (12.5%) as shown in (**Table 4.8)**

Table (4.8): Subtypes of Hodgkin lymphoma.

Hodgkin lymphoma subtype	Frequency	Percentage%
Lymphocyte rich type	3	12.5%
Mixed cellularity	11	45.83%
Nodular sclerosis	9	37.5%
Nodular lymphocyte predominant Hodgkin lymphoma	1	4.17%
Total	**24**	**100%**

4.6.C. The distribution of Non- Hodgkin lymphoma subtypes: Out of 160 cases, 19 cases were diagnosed as non-Hodgkin lymphoma; DLBCL is the most frequent subtype (47.4%) followed by lymphoblastic lymphoma (15.8%) and marginal zone B cell lymphoma (15.8%) as shown in **(Table 4.9)**.

Table (4.9): The distribution of Non- Hodgkin lymphoma subtypes.

Non - Hodgkin lymphoma subtype	Frequency	Percentage %
Follicular lymphoma	1	5.3%
Lymphoblastic lymphoma	3	15.8%
Small lymphocytic lymphoma	2	10.4%
DLBCL	9	47.4%
T- cell lymphoma	1	5.3%
Marginal zone B cell lymphoma	3	15.8%

Total	**19**	**100%**

4.6.D. Histological type of metastasis: Out of 160 cases, 28 cases were diagnosed as metastasis. Papillary thyroid carcinoma (PTC) (35.6%) followed by squamous cell carcinoma (25%) and nasopharyngeal carcinomas (17.9%) were the most common primary malignancies as shown in **(Table 4.10).**

Table (4.10): Histological type of metastasis.

Metastasis	Frequency	Percentage%
Squamous cell carcinoma	7	25%
Paraganglioma	1	3.6%
Nasopharyngeal carcinoma	5	17.9%
Non-small cell carcinoma	2	7.1%
Clear cell type RCC	1	3.6%
PTC	10	35.6%
Small cell carcinoma	1	3.6%
Neuroblastoma	1	3.6%
Total	**28**	**100%**

4.6.E. The origin of metastasis: Out of 160 cases, 28 cases were diagnosed as metastasis; Thyroid (35.7%) followed by lung (28.5%) and nasopharynx (17.8%) were the most common primary origin of the metastatic malignancy as shown in **(Table 4.11).**

Table (4.11): The origin of metastasis.

Origin of metastatic malignancy	Frequency	Percentage%
Larynx	1	3.6%
carotid body	1	3.6%
Nasopharynx	5	17.8%
Lung	8	28.5%
Tongue	1	3.6%
Kidney	1	3.6%
Thyroid	10	35.7%
Eye	1	3.6%
Total	**28**	**100%**

4.7. Relationship between clinicopathological parameters

4.7.1. Relation between the cause of LAP and the clinical presentation There is a significant relation between the cause of LAP and clinical presentation **(p value = 0.001)** as shown in **(Table 4.12).**

Table (4.12): Relation between the cause of LAP and clinical presentation.

Clinical Presentation	The cause of LAP		P value
	Non neoplastic	Neoplastic	
LAP and other symptoms (fever, weight loss, night sweats)	30.3%	60.6%	**0.001**
Only tender LAP	66.3%	0.0%	
LAP and history of secondary neoplasm	3.4%	39.4%	
Total	100%	100%	

4.7.2. Correlation between histopathological diagnosis and the level of lymph nodes involvement There is a significant a correlation between the histopathological diagnosis and level of lymph node involvement **(p value 0.004)** as shown in **(Table 4.13).**

Table (4.13): Correlation between histopathological diagnosis and the level of lymph nodes involvement.

Diagnosis	Level of involvement							
	I	II	III	IV	V	VI	Multiple levels	Total
Reactive LAP	11 68.8%	11 36.7%	10 28.6%	14 38.9%	3 13.6%	2 25%	5 38.5%	56 35%
TB	1 6.3%	5 16.7%	11 31.4%	6 16.7%	3 13.6%	1 12.5%	1 7.7%	28 17.5%

Toxoplasmosis	0 0%	0 0%	0 0%	1 2.8%	4 18.2%	0 0%	0 0%	5 3.1%
HL	0 0%	5 16.7%	4 11.4%	5 13.9%	6 27.3%	3 37.5%	1 7.7%	24 15%
NHL	2 12.5%	2 6.7%	6 17.1%	4 11.1%	4 18.2%	1 12.5%	0 0%	19 11.9%
Metastasis	2 12.5%	7 23.3%	4 11.4%	6 16.7%	2 9.1%	1 12.5%	6 46.2%	28 17.5%
total	16 100%	30 100%	35 100%	36 100%	22 100%	8 100%	13 100%	160 100%
P value	0.004							

4.7.3. Correlation between histopathological diagnosis and age

There is a significant correlation between histopathological diagnosis and age categories **(p value = 0.004),** Patients under the age of 20 year were more likely to have reactive LAP and Hodgkin lymphoma, but those between the ages of (20 and 29) year were more likely to have tuberculosis. Non-Hodgkin lymphoma (NHL) was most common in patients over 50 year and metastases were most common in those between (40 and 50) year, followed by those over 50 year as shown in **(Table 4.14)**.

Table (4.14): Correlation between histopathological diagnosis and age.

Diagnosis		**Age categories (year)**					**Total**
		<20	**20-29**	**30-39**	**40-50**	**>50**	
Reactive lymphadenopat hy	Count	20	6	5	8	17	56
	Percentage	45.5%	19.4%	22.7%	40.0%	39.5%	35.0%
TB	Count	9	10	5	3	1	28
	Percentage	20.5%	32.3%	22.7%	15.0%	2.3%	17.5%
Toxoplasmosis	Count	2	2	1	0	0	5
	Percentage	4.5%	6.5%	4.5%	0.0%	0.0%	3.1%
HL	Count	10	7	3	0	4	24
	Percentage	22.7%	22.6%	13.6%	0.0%	9.3%	15.0%
NHL	Count	1	2	3	2	11	19
	Percentage	2.3%	6.5%	13.6%	10.0%	25.6%	11.9%
Metastasis	Count	2	4	5	7	10	28
	Percentage	4.5%	12.9%	22.7%	35.0%	23.3%	17.5%
Total	Count	44	31	22	20	43	160
	Percentage	100%	100%	100%	100%	100%	100%
P value				0.004			

4.7.4. Relation between the final histopathological diagnosis and size

There is a significant relation between the final histopathological diagnosis and the size of enlarged lymph nodes, reactive nodes were < 2cm in size while all other cases ranged mainly 2-5 cm in size, only 6 cases were > 5cm in size and they were mainly metastatic **(p value =0.002)**; as shown in **(Table 4.15).**

Table (4.15): Relation between the final histopathological diagnosis and size.

Size					
	Diagnosis		**<2**	**2-5**	**>5**
	Reactive lymphadenopathy	Count	28	27	1
		Percentage	58.3%	25.5%	16.7%
	TB	Count	6	22	0
		Percentage	12.5%	20.8%	0.0%
	Toxoplasmosis	Count	1	4	0
		Percentage	2.1%	3.8%	0.0%
	HL	Count	6	17	1
		Percentage	12.5%	16.0%	16.7%
	NHL	Count	3	16	0
		Percentage	6.3%	15.1%	0.0%
	Metastasis	Count	4	20	4

		Percentage	8.3%	18.9%	66.7%
Total		Count	48	106	6
		Percentage	100%	100%	100%
P value		0.002			

4.7.5. Relation between final histopathological diagnosis and number of enlarged lymph nodes

There is a significant relation between final histopathological diagnosis and number of enlarged lymph nodes **(p value= 0.002).** Reactive lymphadenopathy, TB and metastasis had multiple node enlargement, while lymphomas had single node enlargement as shown in **(Table 4.16).**

Table (4.16): Relation between final histopathological diagnosis and number of enlarged lymph nodes.

Number of enlarged nodes				**Total**
Diagnosis		**multiple**	**single**	
Reactive lymphadenopathy	Count	31	25	56
	Percentage	32.6%	38.5%	35.0%
TB	Count	19	9	28
	Percentage	20.0%	13.8%	17.5%
Toxoplasmosis	Count	3	2	5
	Percentage	3.2%	3.1%	3.1%
HL	Count	10	14	24
	Percentage	10.5%	21.5%	15.0%
NHL	Count	7	12	19
	Percentage	7.4%	18.5%	11.9%
Metastasis	Count	25	3	28
	Percentage	26.3%	4.6%	17.5%
Total	Count	95	65	160
	Percentage	100%	100%	100%
P value	0.002			

4.7.6. Correlation between final histopathological diagnosis and duration of LAP

There is a significant correlation between final histopathological diagnosis and duration of LAP **(P value= 0.0001).** Reactive nodes had acute duration while TB, toxoplasmosis, lymphomas and metastatic cases all had chronic duration as shown in **(Table 4.17).**

Table (4.17): Correlation between final histopathological diagnosis and duration of LAP.

Duration					
Acute				**Chronic**	**Total**
Diagnosis	**Reactive lymphadenopathy**	Count	32	24	56
		Percentage	94.1%	19.0%	35.0%
	TB	Count	1	27	28
		Percentage	2.9%	21.4%	17.5%
	Toxoplasmosis	Count	1	4	5
		Percentage	2.9%	3.2%	3.1%
	HL	Count	0	24	24
		Percentage	0.0%	19.0%	15.0%
	NHL	Count	0	19	19
		Percentage	0.0%	15.1%	11.9%
	Metastasis	Count	0	28	28
		Percentage	0.0%	22.2%	17.5%
Total		Count	34	126	160
		Percentage	100.0%	100.0%	100.0%
P value		0.0001			

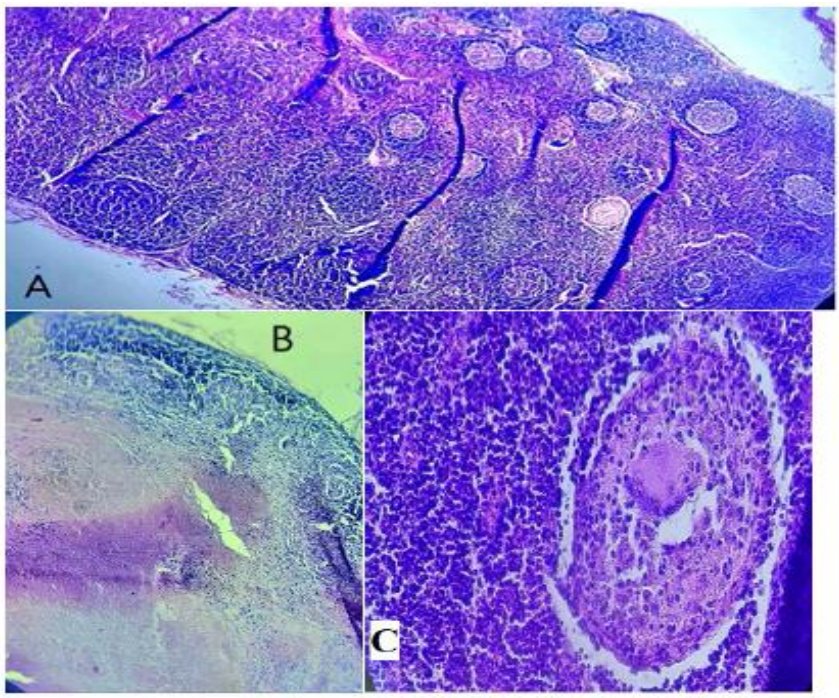

Figure (4.6): Microphotograph of Tuberculosis lymphadenitis: showing multiple granulomas, (A) H&E, 4x, with large area of necrosis, (B) H&E, 4x, aggregation of epithelioid histiocytes with multinucleated giant cell and lymphocytes, (C) H&E,40x.

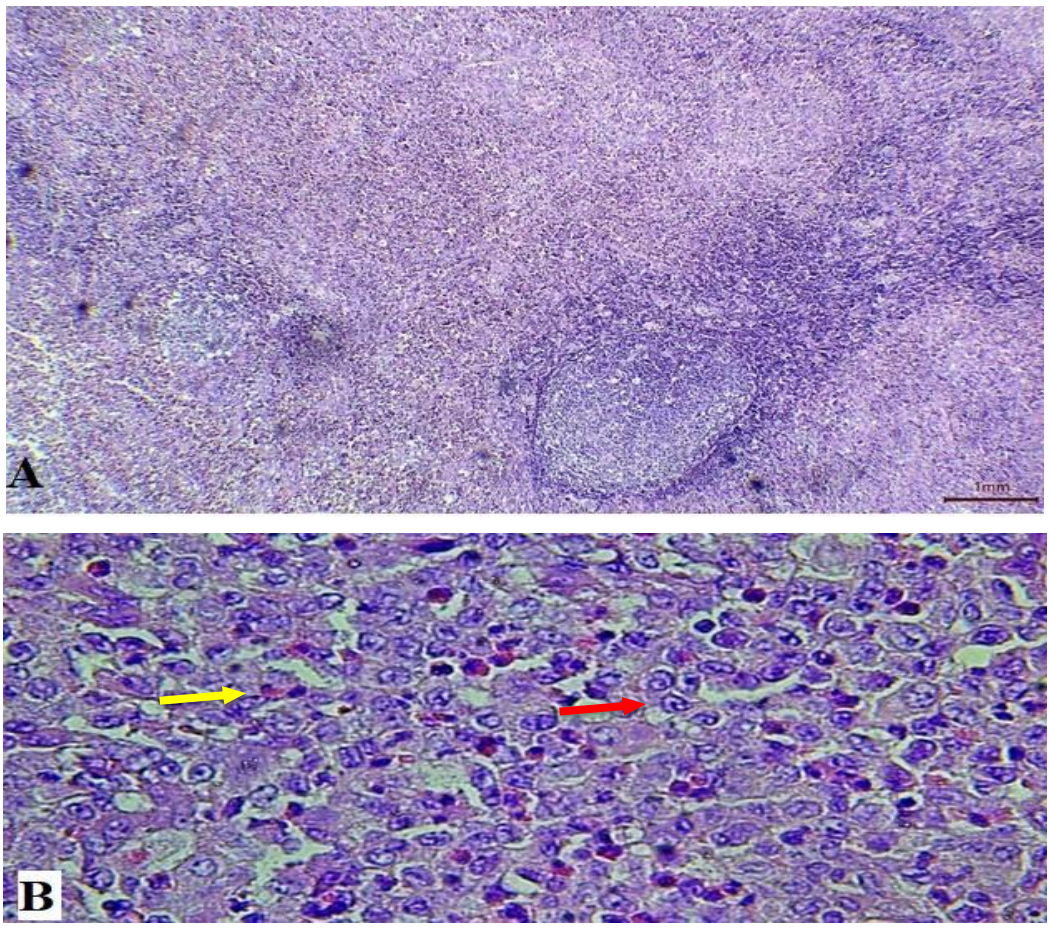

Figure (4.7): Microphotograph of Langerhans cell histiocytosis: showing partial effacement of architecture with preservation of some follicular centers, (A) H&E,4x, at high power showing eosinophil rich lesion (yellow arrow) with admixed large Langerhans cell histiocyte abundant pale to pink cytoplasm, folded nuclei and coffee bean shaped nuclear grooves (red arrow), H&E,40x (B).

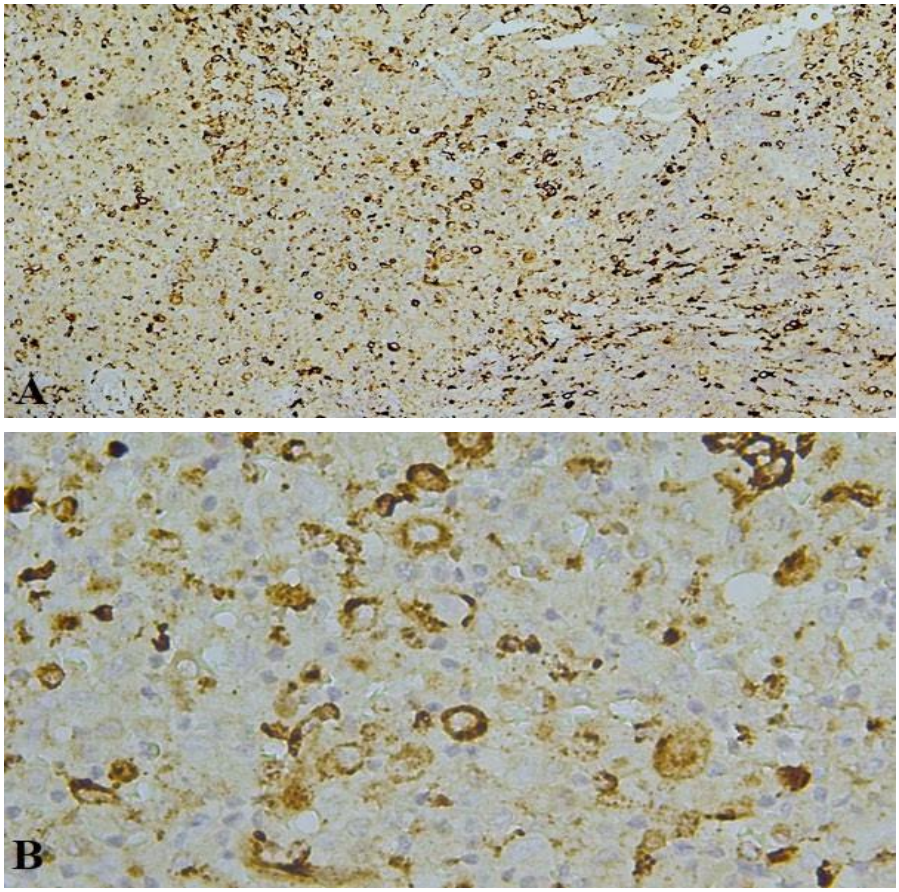

Figure (4.8): Microphotograph of Langerhans cell histiocytosis: showing membranous staining of CD1a immunostaining in typical Langerhans cells (A at 10x, B at 40x).

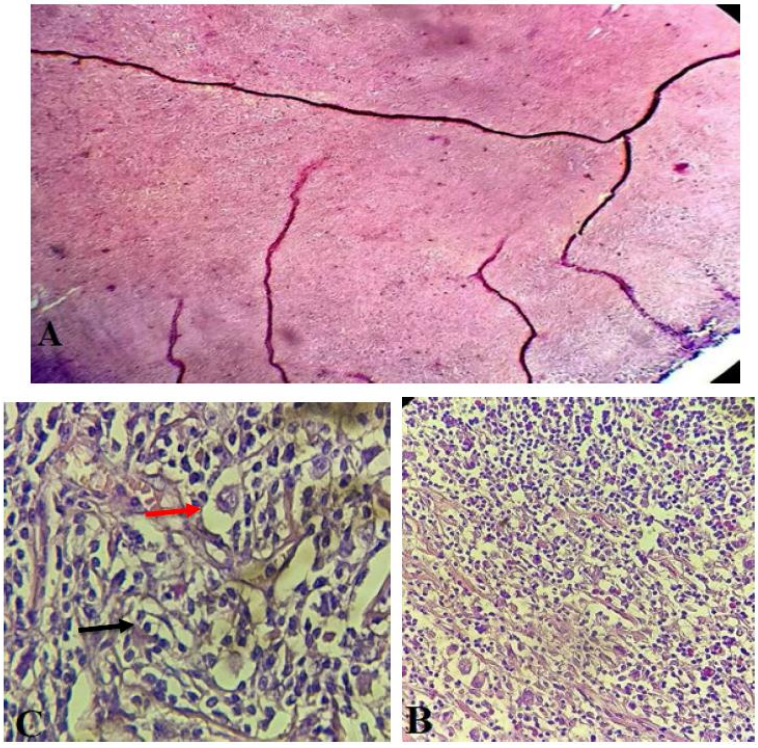

Figure (4.9): Microphotograph of Hodgkin lymphoma – mixed cellularity subtype showing complete effacement of architecture with scattered Reed-Sternberg and Hodgkin cells in polymorphous background comprised of many lymphocytes (black arrow), eosinophils and histiocytes, Reed-Sternberg cells (red arrow), (H&E,4x A, 10x B and 40x C).

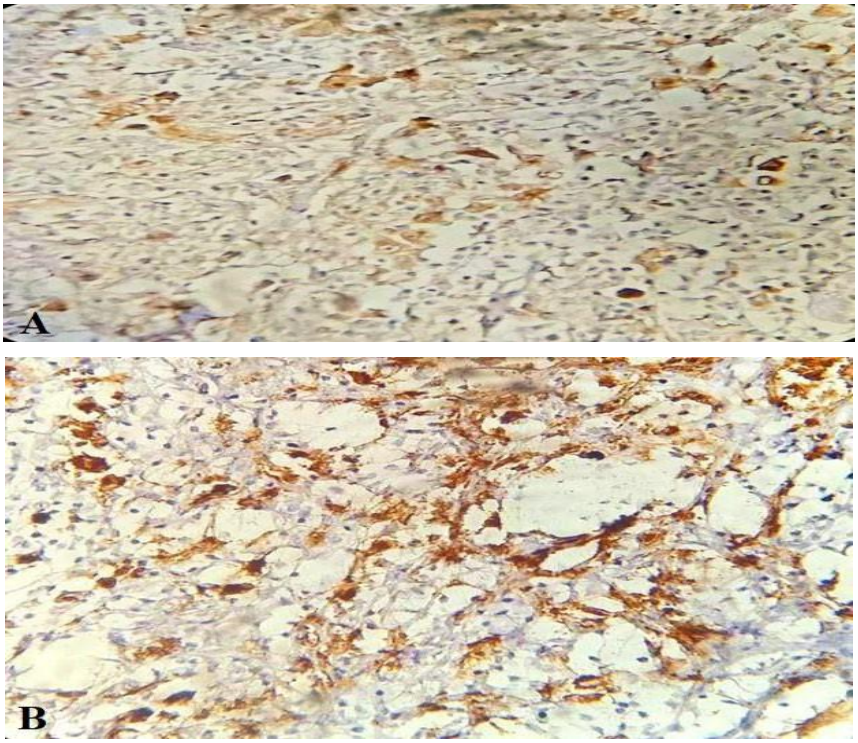

Figure (4.10): Microphotograph of Hodgkin lymphoma – mixed cellularity subtype showing cytoplasmic and membranous reactivity for CD30, (A) 10x and reactivity for CD15, (B) 40x of Reed-Sternberg cells.

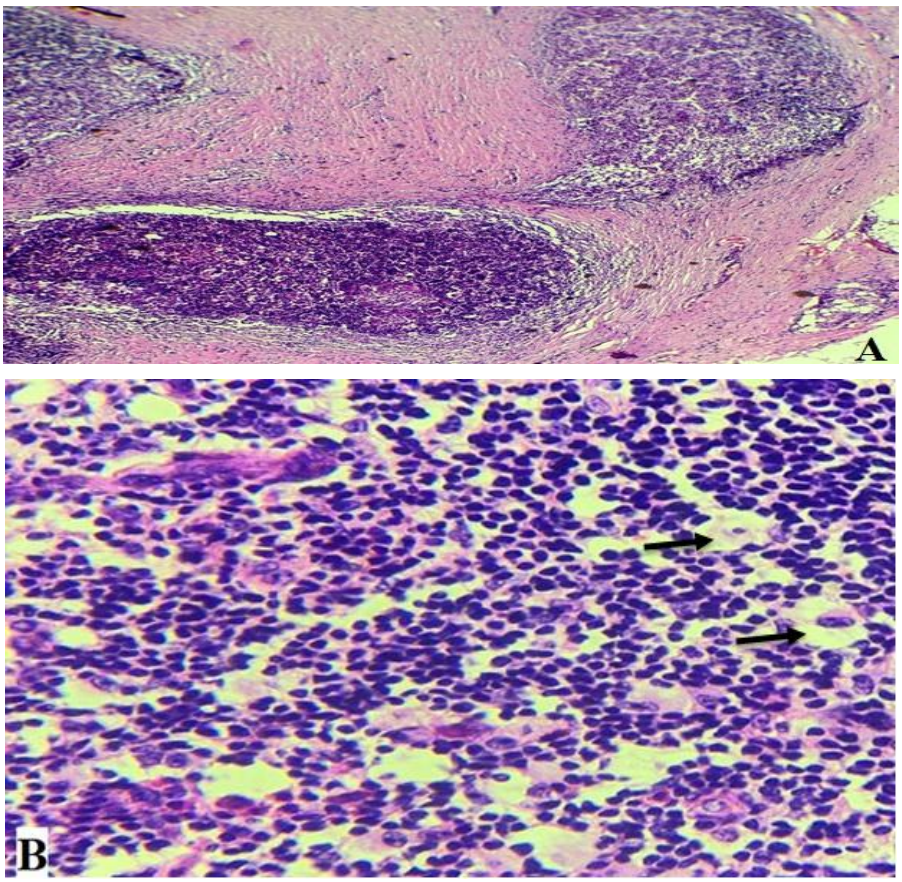

Figure (4.11): Microphotograph of Hodgkin lymphoma - nodular sclerosis subtype showing bands of dense fibrosis creating a nodular growth pattern, H&E,4x (A). Lobulated nuclei, pale retracted cytoplasm, creating lacunae-like spaces (arrow) with mixed inflammatory background like small lymphocytes and histiocytes, H&E,40x (B).

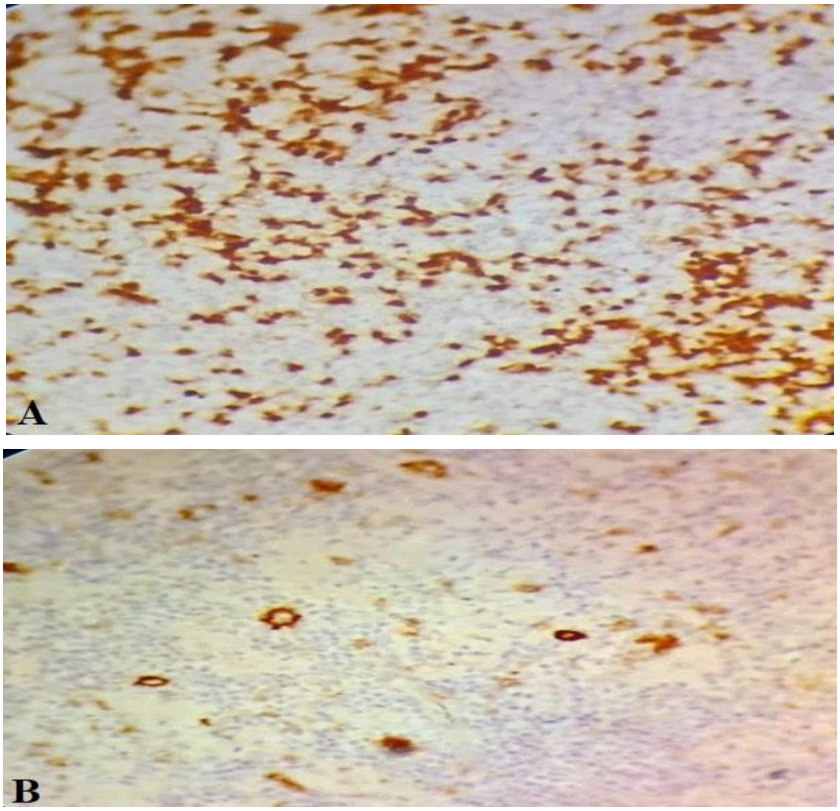

Figure (4.12): Microphotograph of Hodgkin lymphoma - nodular sclerosis subtype showing A nuclear reactivity of neoplastic cells for Pax5 and cytoplasmic and membranous reactivity for CD30 (A at 40x, B at 10x).

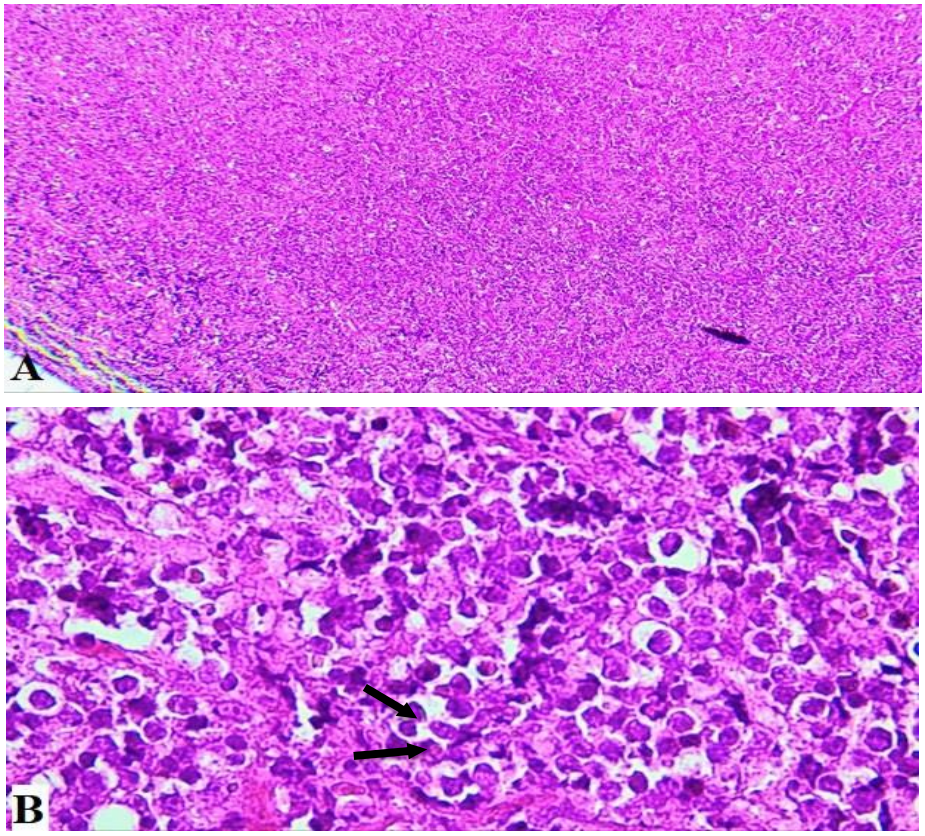

Figure (4.13): Microphotograph of non- Hodgkin lymphoma, diffuse large B cell lymphoma showing complete effacement of the normal tissue architecture by a diffuse infiltrate of large atypical lymphoid cells ,(A) H&E,4x. In high power showing large atypical lymphoid cells with pleomorphic nuclei, prominent nucleoli and vesicular chromatin (arrow), (B) H&E, 40x.

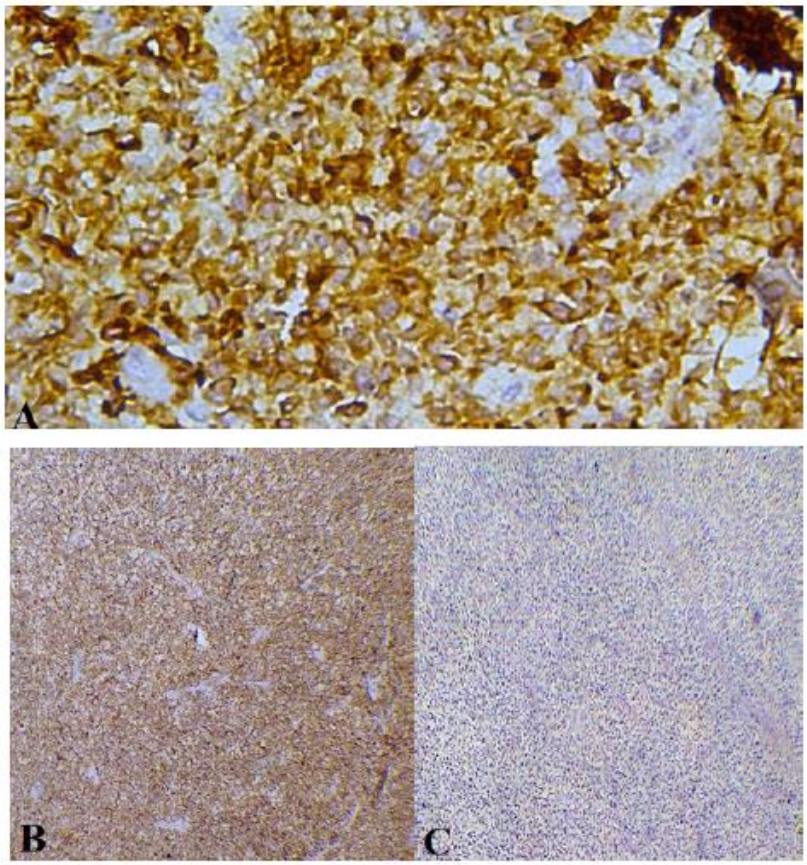

Figure (4.14): Microphotograph of non- Hodgkin lymphoma, diffuse large B cell lymphoma showing B cell lymphocytes, strong Bcl2 positive (membrane and cytoplasmic staining), and positivity for CD 20 and Mum 1 negative (A at 40x, B and C at 10x).

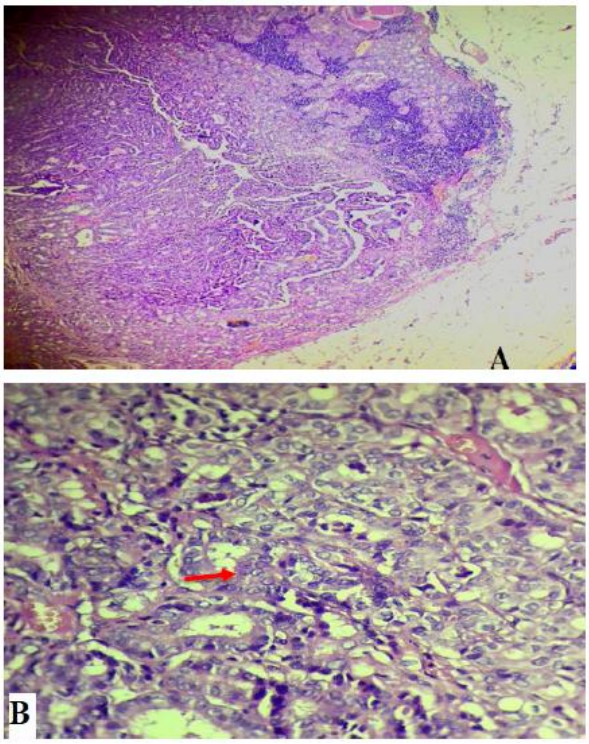

Figure (4.15): Microphotograph of Metastatic papillary thyroid carcinoma in lymph node: showing effacement of architecture in papillary and follicular growth pattern with residual lymphoid tissue and penetration of capsule , H&E,4x (A), and showing nuclear enlargement, crowding / overlapping, clearing and grooves (red arrow) at H&E,40x (B).

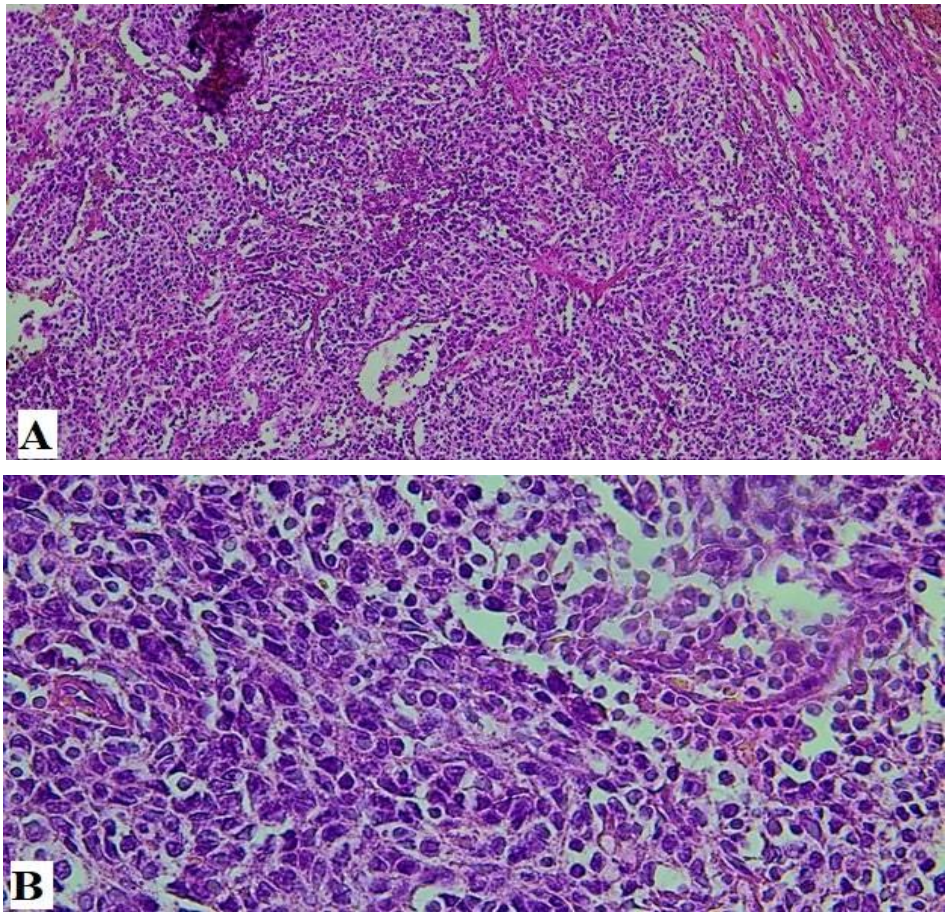

Figure (4.16): Microphotograph of Metastatic nasopharyngeal carcinoma in lymph node: showing cohesive growth pattern, with the islands of tumor sharply demarcated from the surrounding stroma, H&E,10x (A), the tumor cells typically have an indistinct cellular outline and distinct nucleoli, H&E,40x (B).

DISCUSSION

This study showed a mean age of 31 year, patients under the age of 20 year were the most prevalent age group in this study, followed by those over 50 year. This is consistent with findings from Motiwala et al., who found that the age range of (13 to 20 years old) accounted for 39.13% of cases.[69] Gorle et al. observed that a significant percentage of cases (73%) occurred in individuals aged (12 to 40 year), with a peak frequency in the age bracket of (21 to 30 years), (36%).[70] The majority of occurrences (32%), according to other research like Mukherjee and Vikram, were in people aged (21 to 30 year).[71]

Age and diagnosis were found to be significantly correlated (p = 0.004). Patients under the age of 20 year are more likely to present with reactive lymphadenopathy (LAP) and Hodgkin lymphoma (HL). In contrast, individuals aged (20 to 29 year) exhibit a higher incidence of tuberculosis as a cause of LAP. Non-Hodgkin lymphoma (NHL) predominantly affects patients over the age of 50 year, reflecting the increased prevalence of this malignancy in older populations. Metastatic involvement of lymph nodes is most commonly observed in patients aged (40 to 50 year), with a second peak in individuals over 50 years. Similarly, Fahim et al. (2020) in Egypt found that malignancies had higher mean ages (41.4 ± 19.5) than reactive lymph nodes (25.05 ± 19.9), indicating a significant age-related difference (p = 0.005).[72] While Naeimi et al. (2009) discovered that lymphoma was the most prevalent malignant lymphadenopathy among patients under 40 year[37], Alkumasi et al (2018), also found that TB was more prevalent in the young age group (the mean age was 27.7years±SD 15.3).[73] Other research, including Shakya (2009), noted that the fifth decade was when the prevalence of cancer peaked.[74]

Males were more than females in this study and they made (59.38%) of the cases with male to female ratio of 1.46:1 , this finding agrees with research by Mukherjee and Vikram, who reported a male to female ratio of 1.38:1[71], and Rahman et al (2023), which found that 58% of cases were male.[75] Similarly, Inamdar and Gorle et al. (2018) noted a male to female ratio of 1.22:1.[70] In India, Veetil et al (2020) found that the male to female ratio was 1.38:1, indicating a male predominance.[76] On the other hand, Alkumasi et al (2018) found that women made up 56.7% of the patients in Iraq, resulting in a male to female ratio of 1:1.3.[74]

In regard to symptoms other than cervical LAP. LAP with systemic symptoms such as fever, weight loss, and night sweats (43.8%), tender LAP (36.9%), LAP with a

history of secondary neoplasm (19.3%) were the most frequent clinical presentations. Rahman et al (2023) found that fever was the most frequent accompanying symptom to LAP (57.5%).[75] Motiwala et al. also noted that the most common symptoms were fever (60%) and weight loss (46.96%).[69] Ashrafozzaman et al (2019) noted that fever, weight loss, and overall weakness are the commonest symptoms, with fever being especially important in cases of lymphoma and tuberculosis.[77]

Regarding the levels of involved lymph node group, the lower jugular group (Level IV) had the highest prevalence of lymphadenopathy in this study (22.5%), followed by the middle jugular group (Level III) (21.9%), the upper jugular group (Level II) (18.8%) and the posterior triangle group (Level V) (13.8%).

Similarly, Naeimi et al. (2009) in Iran found that the posterior chain group (Level V) (20.8%) and the jugulodigastric group (Level II) (30.5%) were the most frequently affected nodes.[37]

The group with the most affected was the posterior triangle (Level V) (32%) in Egypt, followed by the middle jugular (Level III) (26%) and the upper jugular (Level II) (19%), according to Fahim et al. (2020).[72]

According to David et al. (2017), the middle jugular group (Level III) was affected 21% of the time, while the upper jugular group (Level II) was most frequently affected (26%).[78] In Iraq, Alkumasi et al. (2018) found that the spinal accessory group (part of Level V) had the second-highest participation (36.7%), after the upper jugular group (Level II) (43.3%).[73] Additionally, Bhadouriya et al. (2016) noted that the posterior triangle group (Level V) and upper deep jugular group (Level II) were frequently involved.[79]

According to these results, although there may be some variations, cervical nodes in the jugular chain (Levels II–IV) and the posterior triangle (Level V) are more frequently affected by cervical lymphadenopathy.

In this study, the majority of enlarged lymph nodes (66.25%) measured between (2-5) cm in size. Smaller nodes, measuring less than 2 cm, accounted for 30% of cases, while a minority (3.75%) exhibited sizes greater than 5 cm. Similarly, Bhadouriya et al. (2016) found that the majority of nodes (86.5%) were <3 cm.[79] The most common size of enlarged cervical lymph nodes, according to Mansoor et al. (2002) in Saudi Arabia, was roughly 3 cm.[80]

Approximately 59% of cases of lymphadenopathy (LAP) involved the enlargement of multiple lymph nodes, rather than a single swollen node. Furthermore, 78.75% of cases were characterized by a chronic duration. The consistency of the enlarged nodes was predominantly firm in 62.5% of cases. Additionally, 53.68% of cases involved discrete nodes grossly.

Ashrafozzaman et al (2019) found that the majority of lymph nodes in Bangladesh were mobile, firm in consistency, discrete, and non-tender.[77] According to Miah et al. (2007), 92% of lymph nodes were hard.[81]

According to Bhadouriya et al (2016), 81.1% of patients had single node involvement, whilst 21.7% of cases had matting.[79] 30% of patients in Iraqi study had a chronic duration LAP, according to Alkumasi et al(2018).[73]

Variations in the underlying etiology and patient population can be the reason for the variances in lymph node number and consistency between this study and others. Nodes become firmer as a result of fibrosis and encapsulation when chronic or malignant diseases are more common. The etiology also affects the variety in the number of affected nodes; for instance, tuberculosis may affect fewer nodes than malignant diseases, which frequently result in multiple node involvement. instances with acute or reactive causes on the other hand, frequently found softer or more movable nodes.[81] As a result, the frequency of single versus multiple node involvement varies throughout research.

In this study, the most frequent histological diagnosis for cervical lymphadenopathy (LAP) was reactive lymphadenopathy, which accounted for 35% of cases. Tuberculosis was the second most common cause, identified in 17.5% of cases.

Other studies such as Shakya et al. discovered that reactive lymphadenopathy was the most common cause (50.4%), followed by tuberculosis (22.4%)[74], Alkumasi et al (Iraq, 2018) also identified reactive hyperplasia (38.3%) and tuberculosis (25%) and as the main causes.[73] Whereas Rahman et al. (2023) claimed that tuberculosis was the primary cause (47%).[75]

According to Motiwala et al., tuberculosis accounted for (54.78%) and reactive causes accounted for (22.61%) of the total etiology.[69] According to Veetil et al. (2020), the most common cause was tuberculosis (44%), followed by malignancies and reactive lymphadenitis (30%).[76]

The variation in disease prevalence can be attributed to geographical factors, as well as differences in study populations and design. Malignancies are observed to be more prevalent in specialist healthcare centers, whereas tuberculosis (TB) is frequently reported as the primary cause of disease in regions with high TB prevalence.

Compared to non-neoplastic causes of lymphadenopathy were found to be more prevalent, accounting for 55.63% of cases, compared to neoplastic causes, which comprised 44.38%. According to Veetil et al (India, 2020), non-neoplastic lesions were responsible for (76%) of cervical LAP cases.[76]

Regarding lymphomas were diagnosed in 26.9% of the patients, with Hodgkin lymphoma (HL) accounting for 15% and non-Hodgkin lymphoma (NHL) comprising 11.9%. Among the HL subtypes, mixed cellularity was the most prevalent, representing 45.83% of cases, followed by nodular sclerosis at 37.5%. Regarding NHL subtypes, diffuse large B-cell lymphoma (DLBCL) was the most common, accounting for 47.4% of cases, while marginal zone B-cell lymphoma and lymphoblastic lymphoma each constituted 15.8%. These results align with other studies like Alkumasi et al. (2018) which found lymphomas in 21.7% of patients, with NHL (61.5%) more common than HL (38.5%).[73] Fahim et al. (2020) also reported more cases of HL than NHL.[72]

Additionally, Ibrahim and Sayed (KSA) discovered that HL was the most common type of lymphoma.[82] Naeimi et al. (2009) found that HL was the most common lymphoma subtype, accounting for two-thirds of cases.[37] And According to Mansoor et al. (2002), nodular sclerosis is the most prevalent HL while in the present study, mixed cellularity was the most common subtype of HL.[80]

On the other hand, Mukherjee and Vikram and Rahman et al. (2023) observed that NHL predominance was seen in 75% of lymphoma cases, respectively.[71][75] Hirachand et al. determined that NHL accounted for 33.33% and HL for 13.33% of all malignancies[83], while Veetil et al. (2020) reported a 3:1 ratio of NHL to HL. Unlike our distribution[76], NHL and HL have equal distributions (15.79% each), according to David et al. (2017).[78]

Certain lymphoma subtypes, such as diffuse large B-cell lymphoma (DLBCL) or mixed cellularity Hodgkin lymphoma, may be more common in areas with higher Epstein-Barr virus (EBV) or human immunodeficiency virus (HIV) infection rates. Furthermore, Studies claiming a higher predominance of NHL (e.g., Rahman et al. and Veetil et al.) may reflect regional epidemiology or variations in referral patterns.

In this study, 28 individuals had metastatic lymphadenopathy, with the most prevalent metastatic malignancy was papillary thyroid carcinoma (PTC) at (35.6%), and followed by squamous cell carcinoma at (25%) and nasopharyngeal carcinoma at (17.9%). Similarly, Biswas et al. discovered that squamous cell carcinoma was the most frequent type of metastatic cancer (8.5%), followed by adenocarcinoma (7.8%)[7]. Khajuria et al. also noted that undifferentiated carcinoma, adenocarcinoma, and squamous cell carcinoma are prevalent metastatic cancers.[84]

Thyroid (35.7%) followed by lung (28.5%) and nasopharynx (17.8%) were the most common primary origin of the metastatic malignancy, this finding aligns with other studies such as Pavlidis et al (2009), which also reported metastases from head and neck malignancies, specifically p16-positive oropharyngeal cancer, thyroid papillary cancer, and squamous cell carcinomas of oral and hypopharyngeal cancers, account for the majority of neoplastic causes of cervical lymphadenopathy.[85]

And Mansoor et al. (2002) reported metastatic lymphadenopathy mainly from squamous cell carcinoma originating in the larynx and oropharynx/hypopharynx.[80] Disparities in regional cancer epidemiology and diagnostic capacities are reflected in the variation in metastatic patterns.

6.1. CONCLUSIONS

1. Majority of cervical lymphadenopathy in the current study are benign.
2. Reactive follicular hyperplasia is the most commonly observed benign histological finding in cases of cervical lymphadenopathy (LAP).
3. Hodgkin lymphoma (HL) is the most prevalent form of lymphoma than non- Hodgkin lymphoma. Mixed cellularity emerged as the most common subtype of HL, followed by nodular sclerosis.
4. Patients under the age of 20 years were more likely to have reactive LAP and Hodgkin lymphoma.
5. Papillary thyroid carcinoma (PTC) represents the most common primary malignancy of the thyroid gland that metastasize to cervical lymph nodes Following PTC, squamous cell carcinoma of the lung is the second most frequent source of metastasis.

6.2. Recommendations

1. A multicenter study with a larger sample size could provide a more comprehensive evaluation of cervical lymphadenopathy.
2. Given the variety of potential causes of cervical lymphadenopathy, many of which are associated with serious health conditions, it is essential to conduct thorough investigations in all cases presenting with this symptom.
3. Linking presurgical imaging with histopathologic analysis may aid in improving diagnostic accuracy.

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النتائج:

تضمنت الدراسة تضخم الغدد اللمفاوية العنقي بين 160 مريضًا، وكشفت أن الفئات العمرية الأكثر شيوعًا كانت أقل من 20 عامًا وأكثر من 50 عامًا، بمتوسط عمر 31 عامًا. كان عدد المرضى الذكور أعلى قليلاً من الإناث بنسبة 1.46:1. كان العرض السريري الأكثر شيوعًا هو تضخم الغدد اللمفاوية المصحوب بأعراض جهازية مثل الحمى، وفقدان الوزن، والتعرق الليلي (43.8%)، مع استمرار الحالة المزمنة في (78.7%) من الحالات. أظهر المستوى الرابع من الغدد اللمفاوية العنقية أعلى معدل انتشار (22.5%). وكانت معظم الغدد المتضخمة يتراوح حجمها بين 2-5 سم (66.25%)، مع وجود عدة عقد لمفاوية في (59.4%) من الحالات. من الناحية الشكلية، كانت (53.68%) من الغدد اللمفاوية منفصلة، و(62.5%) أظهرت قوامًا صلبًا. كان تضخم الغدد اللمفاوية التفاعلي هو السبب الأكثر شيوعًا (35%) ويليه السل (17.5%). وشكلت الأورام اللمفاوية من نوع هودجكين (15%) من الحالات، وكان النمط الأكثر شيوعًا هو التشكيل الخلوي المختلط (45.83%)، يليه التصلب العقيدي (37.5%). ومثلت الأورام الليمفاوية نوع لاهودجكين (11.9%) من الحالات، وكان النمط السائد (47.4%) هو الورم الليفي من نوع الخلايا البائية الكبيرة المنتشرة.

بالنسبة لتضخم الغدد اللمفاوية النقائلي: تم تشخيصه في (17.5%) من الحالات، وكانت أكثر مصادر النقائل شيوعًا هو سرطان الغدة الدرقية الحليمي (35.6%) ويليه سرطان الخلايا الحرشفية في الرئة (25%).

الاستنتاج:

اظهرت الدراسة ان غالبية حالات تضخم الغدد اللمفاوية العنقية هي حميدة. كان فرط التنسج الجريبي التفاعلي هو النتيجة النسيجية الحميدة الاكثر شيوعا في حالات تضخم الغدد اللمفاوية العنقية.

كان الورم نوع هودجكين الشكل الاكثر انتشارا بين الاورام اللمفاوية، وكان النمط الخلوي المختلط هو النوع الفرعي الاكثر شيوعا ويليه التصلب العقيدي.

اما بالنسبة للاورام الخبيثة الاولية التي انتشرت الى الغدد اللمفاوية العنقية، فقد كان سرطان الغدة الدرقية الحليمي الاكثر شيوعا، يليه سرطان الخلايا الحرشفية في الرئة.

الخلاصة

المقدمة:

تضخم الغدد اللمفاوية هو عملية مرضية تصيب الغدد اللمفاوية وتظهر زيادة غير طبيعية في الحجم أو تغيير في القوام أو العدد. يشير تضخم الغدد اللمفاوية العنقية إلى وجود أنسجة عقدية عنقية يتجاوز حجمها 1 سم في القطر. وهو علامة على وجود مرض أساسي يتراوح من عدوى بسيطة إلى ورم خبيث نقائلي. يمكن تصنيف تضخم الغدد اللمفاوية العنقية حسب مسبباته إلى تفاعلي ونقائلي و ورمي. تُعد الغدد اللمفاوية العنقية موقعًا شائعًا لنقائل لأورام خبيثة من مواقع أخرى، بما في ذلك الجهاز التنفسي والهضمي العلوي والمناطق خلف الأنف وفوق الترقوة. يُصنف تضخم الغدد اللمفاوية العنقية كذلك حسب المدة الزمنية إلى: حاد (مدة أسبوعين)، تحت الحاد (2-6 أسابيع) ومزمن (لا يختفي بعد 6 أسابيع).

الهدف من الدراسة:

تقييم العلاقة بين مختلف المعايير السريرية والمرضية لتضخم الغدد اللمفاوية العنقية مع التشخيص النهائي بواسطة الفحص النسيجي المرضي. تشمل المعايير السريرية المرضية (العمر، الجنس، المدة الزمنية، الاعراض السريرية المرافقة، الموقع، التشريح الحياني، التشخيص (ورمي أو غير ورمي)، الورم الأولي (ليمفوما) مقابل الورم الثانوي (نقائل)، نوع النسيج المرضي للورم الأولي والنقائلي.

المواد وطريقة العمل:

تم إجراء دراسة بأثر رجعي على 160 مريضًا تم اختيارهم عشوائيًا ممن يعانون من تضخم الغدد اللمفاوية العنقية. تم جمع العينات من المختبر التعليمي لمدينة الإمامين الكاظمين(ع) الطبية، وشعبة المختبرات التعليمية في مستشفى غازي الحريري للجراحات التخصصية والمركز الوطني للمختبرات التعليمية لدائرة مدينة الطب ، خلال الفترة من كانون الثاني 2024 الى كانون الاول 2024، تم جمع العينات بين الفترة من كانون الثاني 2018 الى كانون الاول 2023 . تم جمع السرائح وتقارير الفحص النسيجي لكل حالة وإعادة فحصها. كما تم استخراج المعايير السريرية والمرضية من تقارير علم الأمراض الخاصة بالمرضى مثل (العمر، الجنس، المدة الزمنية ، الاعراض السريرية المرافقة ، الموقع، التشريح الحياني ، التشخيص (ورمي أو غير ورمي)، الورم الأولي (ليمفوما) مقابل الورم الثانوي (نقائل)، نوع النسيج المرضي للورم الأولي والنقائلي. تم استبعاد العينات التي تحتوي على بيانات غير كافية عن المرضى.