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Clinical Profile of Cervical Lymph Node Enlargement in Adults: A Comprehensive Prospective Observational Analysis.

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Abstract

Background: Cervical lymphadenopathy is a ubiquitous clinical presentation in adult medicine, representing a diagnostic challenge due to its highly diverse etiological spectrum. Unlike pediatric populations where reactive hyperplasia predominates, adult cervical lymphadenopathy frequently heralds severe underlying pathology, most notably chronic granulomatous infections (such as tuberculosis) and malignant neoplasms (including metastatic carcinomas and primary lymphomas). The ability to rapidly differentiate between benign, infectious, and neoplastic etiologies is critical for initiating timely pharmacological or surgical interventions. ***Objective:*** To systematically evaluate the clinical profile, anatomical distribution, etiological spectrum, and diagnostic yield of clinical and pathological investigations in adult patients presenting with cervical lymph node enlargement. Furthermore, this study aims to define the pharmacological implications of accurate early diagnosis, particularly concerning antimicrobial stewardship and oncological therapeutic planning. ***Methods:*** This prospective observational clinical study evaluated a standardized cohort of 85 consecutive adult patients (≥18 years) presenting with unexplained cervical lymphadenopathy of at least two weeks' duration at a tertiary care academic center. Comprehensive documentation included clinical history, detailed nodal mapping, laboratory investigations, Fine Needle Aspiration Cytology (FNAC), Cartridge Based Nucleic Acid Amplification Test (CBNAAT), and Excisional/Core Needle Histopathological Examination (HPE). Multivariable binary logistic regression was executed to identify independent clinical predictors of malignancy. ***Results:*** The study cohort (N = 85) comprised 48 males (56.5%) and 37 females (43.5%) with a mean age of 46.2±14.8 years. Non-neoplastic etiologies accounted for 64.7% (n = 55) of cases, predominantly driven by tuberculous lymphadenitis (44.7%, n = 38) and reactive lymphoid hyperplasia (14.1%, n=12). Neoplastic etiologies were confirmed in 35.3% (n = 30) of patients, comprising metastatic carcinoma (28.2%, n = 24) and primary lymphoma (7.1%, n=6). Metastatic squamous cell carcinoma (SCC) was the dominant malignant subtype. Level II (Jugulodigastric) was the most frequently involved anatomical site. Hard consistency (OR = 5.92, 95% CI: 2.31–13.88, p < 0.001), fixation to underlying fascia (OR = 4.85, 95% CI: 1.95–11.62, p < 0.001), and age > 50 years (OR = 3.65, 95% CI: 1.62–8.10, p = 0.002) were independent predictors of malignancy. FNAC demonstrated a diagnostic sensitivity of 88.5% and specificity of 95.8% for detecting malignancy. ***Conclusion:*** Tuberculous lymphadenitis and metastatic squamous cell carcinoma constitute the overwhelming burden of adult cervical lymphadenopathy. Detailed clinical phenotyping specifically assessing nodal consistency, fixation, and patient age enables rapid risk stratification. The integration of FNAC and molecular diagnostics (CBNAAT) is paramount for guiding immediate pharmacological therapies, particularly in optimizing anti-tubercular regimens and avoiding inappropriate empirical antibiotic use.

Keywords: Cervical lymphadenopathy, Fine Needle Aspiration Cytology (FNAC), Neck Mass, Lymph Node Enlargement, Histopathological Examination.

INTRODUCTION

The human lymphatic system is an intricate and vital component of the immune and circulatory systems, comprising a vast network of lymphatic vessels, lymphoid tissues, and approximately 800 discrete lymph nodes. The cervical region is exceptionally dense with lymphoid tissue, housing over 300 lymph nodes. These nodes act as dynamic biological filters, trapping antigens, foreign particles, and malignant cells traversing the lymphatic fluid draining from the head, neck, upper respiratory tract, oral cavity, and indirectly, distant infraclavicular structures.[1]

Cervical lymphadenopathy defined clinically as the abnormal enlargement of one or more cervical lymph nodes (typically >1.0cm in maximum diameter) is not a singular disease entity, but rather a prominent phenotypic manifestation of a broad array of underlying systemic or localized pathologies.[2] The physiological mechanisms governing lymph node enlargement are fundamentally categorized into three processes:

1) Antigenic Proliferation: Clonal expansion of B-lymphocytes within the germinal centers and T-lymphocytes within the paracortical regions in response to local or systemic infections (reactive hyperplasia).
2) Infiltration by Inflammatory Cells: Massive recruitment of macrophages, neutrophils, and multinucleated giant cells, classically seen in suppurative bacterial infections or chronic granulomatous diseases like tuberculosis.
3) Neoplastic Proliferation or Seeding: Primary malignant transformation of resident lymphocytes (Hodgkin and Non-Hodgkin Lymphomas) or the mechanical entrapment and subsequent proliferation of metastatic epithelial or mesenchymal cells (carcinomas and sarcomas). [3-6]

The Adult Diagnostic Paradigm

The clinical approach to cervical lymphadenopathy is heavily dictated by patient demographics. In the pediatric population, cervical adenopathy is overwhelmingly benign, typically reflecting transient, self-limiting viral upper respiratory tract infections or localized bacterial pharyngitis. In stark contrast, adult cervical lymphadenopathy carries a profoundly higher pre-test probability of representing a life-threatening granulomatous infection or an underlying malignancy. [7-9]

In the adult cohort, the differential diagnosis spans a vast pathological continuum:

- Infectious and Granulomatous: Mycobacterium tuberculosis, atypical mycobacteria, pyogenic bacterial lymphadenitis (Staphylococcus, Streptococcus), Toxoplasmosis, Syphilis, and viral etiologies including HIV, Cytomegalovirus (CMV), and Epstein - Barr virus (EBV).
- Malignant Neoplasms: Secondary metastatic carcinomas (predominantly head and neck squamous cell carcinomas [HNSCC], thyroid carcinomas, and distant metastatic adenocarcinomas from pulmonary, gastric, or breast primaries) and primary hematological malignancies.
- Autoimmune and Idiopathic: Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis, Sarcoidosis, Castleman disease, and Kikuchi-Fujimoto disease. [7-9]

Epidemiological Context and Pharmacological Implications

The etiological spectrum of adult lymphadenopathy is heavily influenced by regional epidemiology. In developing nations and endemic zones, tuberculous lymphadenitis remains the undisputed leading cause of peripheral lymphadenopathy. It serves as the most frequent clinical presentation of extrapulmonary tuberculosis. The pharmacological management of this condition requires complex, prolonged multidrug regimens (e.g., Isoniazid, Rifampicin, Pyrazinamide, Ethambutol). The emergence of multidrug-resistant tuberculosis (MDR-TB) necessitates exact diagnostic confirmation, as empirical therapy is no longer viable and can propagate catastrophic epidemiological resistance profiles. [10-11]

Concurrently, there is a rising global incidence of metastatic squamous cell carcinomas presenting as lateral neck masses. This is driven synergistically by traditional risk factors chronic tobacco use and alcohol consumption and the increasing prevalence of high-risk Human Papillomavirus (HPV-16 and HPV-18) infections targeting the oropharyngeal mucosa. Accurate and early diagnosis of metastatic nodal disease is critical; the presence of cervical metastasis halves the overall 5-year survival rate of head and neck cancer patients. Furthermore, establishing the histopathological diagnosis guides the subsequent oncological pharmacology, dictating the use of specific cytotoxic chemotherapies, epidermal growth factor receptor (EGFR) inhibitors, or immune checkpoint inhibitors (e.g., Pembrolizumab, Nivolumab). [12-13]

Given these high clinical stakes, the evaluation of adult cervical lymphadenopathy often poses a formidable diagnostic challenge. Overlapping physical presentations such as the rubbery, non-tender nodes seen in both lymphoma and chronic tuberculosis, or the matted nodes present in both advanced granulomatous disease and metastatic extracapsular spread complicate the bedside assessment. [10]

Therefore, this prospective observational study was designed to systematically analyze a standardized cohort of adult patients. By mapping the clinical profile, anatomical distribution, and etiological spectrum, this research aims to identify independent clinical predictors of malignancy and optimize the diagnostic and pharmacological workflow in a tertiary academic setting.

MATERIALS AND METHODS

Study Design and Ethical Considerations

This prospective, observational clinical study was conducted collaboratively across the Department Otorhinolaryngology and General Surgery at multiple tertiary academic medical institutions over an 18-month period. The study protocol underwent rigorous scrutiny and was formally approved by the Institutional Review Board (IRB) and the Institutional Ethics Committee's of all the academic medical institutions. The research adhered strictly to the ethical tenets established by the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines. Written, informed consent was obtained from all participating patients prior to enrollment, physical examination, and tissue sampling.

Study Population and Cohort Standardization

To ensure rigorous statistical analysis and eliminate low-powered observational bias, the study population was standardized to a fixed cohort size of 85 adult patients (N=85). This sample size was determined a priori to provide adequate statistical power for evaluating the primary etiological distributions and identifying predictive multivariable risk factors within each institutional catchment area.

Inclusion Criteria:

- Adult patients aged ≥18 years.
- Presence of clinically detectable cervical lymph node enlargement, strictly defined as a lymph node >1.0cm in maximum diameter (or > 1.5cm for jugulodigastric nodes).
- Duration of lymphadenopathy persisting for ≥2 weeks (to exclude transient, acute self-limiting viral reactive hyperplasia).
- Patients providing informed consent for clinical evaluation, ultrasound imaging, cytological, and histopathological procedures.

Exclusion Criteria:

- Patients with clinically obvious acute thyroid swellings, parotid or submandibular salivary gland tumors, branchial cleft cysts, or soft tissue mesenchymal neoplasms (e.g., lipomas, schwannomas) masquerading clinically as lymph nodes.
- Patients with previously confirmed and documented head and neck malignancies currently undergoing definitive chemoradiation or surgical therapy.
- Patients actively receiving anti-tubercular therapy (ATT) at the time of presentation.
- Patients with severe, uncorrectable coagulopathies contraindicating invasive tissue sampling.

Clinical Evaluation and Anatomical Mapping

Every enrolled patient (N=85) was subjected to a standardized and exhaustive clinical assessment protocol.

1. Comprehensive Clinical History:

Detailed symptom profiling was conducted, focusing on the exact duration of the swelling, progression rate, and the presence of localized aerodigestive symptoms (dysphagia, odynophagia, hoarseness, persistent cough, oral mucosal ulcerations). Systemic constitutional symptoms were rigorously documented, including unexplained pyrexia, debilitating night sweats, and significant involuntary weight loss (> 10% of total body mass over the preceding 6 months). A detailed habit history regarding cumulative pack-years of tobacco smoking, smokeless tobacco (betel quid) chewing, and chronic alcohol consumption was recorded.

2. Physical Examination and Nodal Characterization:

A complete head and neck physical examination was performed, utilizing indirect laryngoscopy and flexible fiberoptic nasopharyngolaryngoscopy to inspect the hidden mucosal surfaces of the nasopharynx, oropharynx, hypopharynx, and larynx.

Cervical lymph nodes were palpated systematically and mapped according to the internationally recognized Robbins classification system:

- Level I: Submental and Submandibular nodes.
- Level II: Upper Jugular nodes (Jugulodigastric).
- Level III: Middle Jugular nodes (Jugulo-omohyoid).
- Level IV: Lower Jugular nodes.
- Level V: Posterior Triangle nodes (Spinal accessory and Transverse cervical chains).
- Level VI: Anterior Compartment (Pretracheal, Paratracheal).
- Supraclavicular Fossa: Analyzed as a distinct, high-risk anatomical zone.

Physical parameters of the dominant nodes were recorded, including laterality, maximum clinical diameter (measured via digital calipers), consistency (categorized as soft, firm, rubbery, or stony hard), tenderness on palpation, and mobility (classified as freely mobile, matted together into an indistinguishable mass, or fixed tightly to the underlying deep cervical fascia or overlying dermis).

Diagnostic and Pathological Workup
Following clinical phenotyping, a step-wise diagnostic algorithm was employed.

1. Laboratory and Serological Testing:
All patients underwent a baseline complete blood count (CBC), peripheral blood smear, Erythrocyte Sedimentation Rate (ESR), and comprehensive metabolic panel. Serological screening for Human Immunodeficiency Virus (HIV) 1 and 2, Hepatitis B Surface Antigen (HBsAg), and Hepatitis C Virus (HCV) was conducted. The tuberculin skin test (Mantoux test) was administered to all patients without known contraindications.

2. Radiological Imaging:
High-resolution Ultrasonography (USG) of the neck utilizing a 7.5–12 MHz linear array transducer was performed. USG was utilized to assess nodal architecture, specifically evaluating the short-axis to long-axis (S/L) ratio, the preservation or loss of the echogenic fatty hilum, the presence of intranodal cystic necrosis, microcalcifications, and the vascular perfusion pattern on Color Doppler (central hilar vs. peripheral capsular flow).

3. Cytological Evaluation (FNAC and Molecular Testing):
Fine Needle Aspiration Cytology (FNAC) served as the primary diagnostic modality for all 85 patients. FNAC was performed utilizing a 22-gauge to 24-gauge needle attached to a 10 mL syringe mounted in a Cameco syringe pistol. A minimum of three distinct passes were made into the dominant node under strict aseptic conditions. Ultrasound guidance was employed for deep-seated, partially cystic, or perilously situated nodes (e.g., adjacent to the carotid sheath).

The aspirated material was immediately expelled onto clean glass slides. Smears were fixed in 95% ethyl alcohol for Papanicolaou (Pap) staining and air-dried for May-Grünwald-Giemsa (MGG) staining. Crucially, in all cases yielding purulent or caseous necrotic material, additional smears were subjected to Ziehl-Neelsen (ZN) staining to detect acid-fast bacilli (AFB). Furthermore, aspirated material was processed for Cartridge Based Nucleic Acid Amplification Testing (CBNAAT / GeneXpert MTB/RIF) to detect Mycobacterium tuberculosis DNA and simultaneously identify rifampicin resistance, guiding the subsequent pharmacological protocol.

4. Histopathological Examination (HPE):
Excisional lymph node biopsy or core needle biopsy was explicitly reserved and performed when FNAC yielded an inconclusive, non-diagnostic result, when the cytological diagnosis was discordant with the overwhelmingly apparent clinical picture, or when a diagnosis of lymphoma was suspected (as intact nodal architecture and extensive immunohistochemistry [IHC] panels are mandatory for accurate WHO classification of hematological malignancies).

Statistical Analysis Methodology
All clinical and pathological data were compiled and statistically analyzed utilizing IBM SPSS Statistics version 28.0 (Armonk, NY: IBM Corp). Continuous variables were assessed for normal distribution using the Shapiro-Wilk test and subsequently expressed as mean \pm standard deviation (SD). Categorical variables were presented as absolute frequencies (n) and valid percentages (%). Bivariate group comparisons for continuous demographic data were conducted using the independent samples Student's t-test or the non-parametric Mann-Whitney U test, as appropriate. Categorical clinical associations (e.g., consistency vs. etiology) were evaluated utilizing the Pearson Chi-square ($\chi 2$) test or Fisher's exact test for variables with expected cell frequencies < 5. To identify independent clinical predictors of malignancy, variables demonstrating a univariate statistical significance threshold of $p < 0.10$ were integrated into a multivariable binary logistic regression model. Adjusted Odds Ratios (aOR) with corresponding 95% Confidence Intervals (CI) were derived. Standard diagnostic performance metrics (Sensitivity, Specificity, Positive Predictive Value [PPV], Negative Predictive Value [NPV], and overall Accuracy) were computed for FNAC against the final established diagnosis. The threshold for statistical significance was rigidly set at a two-tailed p-value < 0.05.

RESULTS

Baseline Demographic Parameters
The standardized study cohort of 85 adult patients successfully completed the entire diagnostic algorithm. The cohort demonstrated a male preponderance, comprising 48 males (56.5%) and 37 females (43.5%), resulting in a male-to-female ratio of 1.3:1. The mean age of the total population was 46.2±14.8 years, spanning an age range of 18 to 76 years.

A profound biphasic age distribution became immediately apparent when correlating patient age with the final etiological diagnosis. Benign pathologies (predominantly infectious and reactive) clustered densely in younger adult cohorts (18–40 years), whereas malignant etiologies dominated the clinical landscape in patients aged > 50 years ($p < 0.001$). A documented history of chronic tobacco consumption (either smoking cigarettes/bidis or chewing smokeless tobacco/gutka) was present in 45.9% (n=39) of the total cohort. Alarmingly, a positive tobacco history was found in 75.0% (n=18) of all patients ultimately diagnosed with metastatic squamous cell carcinoma, highlighting the severe oncogenic impact of these agents.

Table 1: Baseline Demographic and Symptomatology Profiles (N = 85)

Parameter	Benign Etiology (n=55)	Malignant Etiology (n=30)	Total Cohort (N=85)	p-value
Age (years), Mean \pm SD	37.5±12.1	62.1±9.8	46.2±14.8	**< 0.001**
Age Stratification, n (%)				**< 0.001**
- 18–35 years	27 (49.1%)	2 (6.7%)	29 (34.1%)	
- 36–50 years	19 (34.5%)	6 (20.0%)	25 (29.4%)	
- > 50 years	9 (16.4%)	22 (73.3%)	31 (36.5%)	
Gender, n (%)				0.124
- Male	28 (50.9%)	20 (66.7%)	48 (56.5%)	
- Female	27 (49.1%)	10 (33.3%)	37 (43.5%)	
Habit History, n (%)				
- Tobacco Use (Any form)	16 (29.1%)	23 (76.7%)	39 (45.9%)	**< 0.001**
- Alcohol Consumption	9 (16.4%)	14 (46.7%)	23 (27.1%)	**0.003**
Constitutional Symptoms, n (%)				
- Unexplained Fever	29 (52.7%)	8 (26.7%)	37 (43.5%)	**0.021**
- Significant Weight Loss	14 (25.5%)	19 (63.3%)	33 (38.8%)	**< 0.001**
- Night Sweats	12 (21.8%)	6 (20.0%)	18 (21.2%)	0.846

The Etiological Spectrum

The definitive diagnostic breakdown of the 85 cases revealed that non-neoplastic, benign conditions formed the bulk of the clinical load, accounting for 64.7% (n = 55).

Tuberculous lymphadenitis was the single most dominant pathology across the entire study, diagnosed in 44.7% (n=38) of all patients. **Reactive lymphoid hyperplasia**, representing non-specific inflammatory responses to localized or systemic viral/bacterial antigens, was the second most common benign entity at 14.1% (n=12). Acute suppurative bacterial lymphadenitis was found in 3.5% (n=3), and non-tuberculous granulomatous inflammation (consistent with sarcoidosis or fungal etiologies) was observed in 2.4% (n=2). Conversely, malignant neoplastic etiologies comprised a substantial 35.3% (n = 30) of the cohort. Within this malignant subgroup, **metastatic carcinoma** was overwhelmingly prevalent, affecting 28.2% (n = 24) of the total population (and representing 80.0% of all cancers). The histological subtypes of these metastases were primarily Squamous Cell Carcinoma (SCC) in 22 patients (comprising 91.6% of all metastases) and Metastatic Adenocarcinoma in 2 patients. Endoscopic evaluation and subsequent biopsies localized the primary tumors for the SCC metastases primarily to the oral cavity, base of tongue, pyriform sinus, and glottis.

Primary hematological malignancies accounted for the remaining 7.1% (n = 6) of cases, comprising Non-Hodgkin Lymphoma (NHL, n = 4) and Hodgkin Lymphoma (HL, n = 2).

Table 2: Definitive Etiological Spectrum of Adult Cervical Lymphadenopathy

Diagnostic Category	Specific Etiology	Number of Cases (n)	Percentage of Total Cohort (N=85)
Benign / Non-Neoplastic	**Total Benign**	**55**	**64.70%**
	Tuberculous Lymphadenitis	38	44.70%
	Reactive Lymphoid Hyperplasia	12	14.10%
	Acute Suppurative Lymphadenitis	3	3.50%
	Granulomatous (Non-TB)	2	2.40%
Malignant / Neoplastic	**Total Malignant**	**30**	**35.30%**
	Metastatic Squamous Cell Carcinoma	22	25.90%
	Primary Lymphoma (NHL & HL)	6	7.10%
	Metastatic Adenocarcinoma	2	2.40%

Anatomical Distribution and Physical Nodal Characteristics

Unilateral nodal enlargement was documented in 74.1% (n=63) of cases, while bilateral synchronous involvement occurred in 25.9% (n=22).

Anatomical mapping demonstrated that **Level II (Upper Jugular)** was the most frequently affected site across all pathologies, involved in 44.7% (n = 38) of patients. This was closely followed by Level III (Middle Jugular) at 32.9% (n=28) and Level V (Posterior Triangle) at 23.5% (n=20). Notably, the presence of enlarged nodes in the **Supraclavicular Fossa** (n=11) harbored a profoundly grim prognosis; 81.8% (n=9) of supraclavicular presentations were diagnosed as malignant (representing both lymphoma and distant metastatic adenocarcinoma).

The physical characteristics of the lymph nodes correlated tightly with their ultimate pathological diagnoses:

- **Consistency:** The texture of the node on palpation was a critical diagnostic clue. Nodes described as "stony hard" were almost exclusively malignant; 85.0% of hard nodes were diagnosed as metastatic carcinoma ($p < 0.001$). Soft to firm nodes were the hallmark of reactive hyperplasia and early tuberculosis. Rubbery, discrete, and non-tender nodes were highly suspicious for primary lymphoma.
- **Fixation and Matting:** Tuberculous nodes frequently presented as matted, coalesced masses (observed in 42.1% of TB cases) due to peri-adenitis and capsular breakdown. Fixation of the node to the overlying skin or tethering to the deep muscular fascia was strongly and significantly associated with metastatic carcinoma, indicative of invasive extracapsular spread.
- **Tenderness:** Malignant lymph nodes were characteristically painless and non-tender in 93.3% of cases. Exquisite tenderness was generally reserved for acute suppurative lymphadenitis or rapidly expanding, centrally necrotic tuberculous nodes.

Table 3: Correlation of Physical Nodal Characteristics with Pathological Outcome

Physical Attribute	Benign (n=55)	Malignant (n=30)	p-value
Clinical Size (Max Diameter)			**0.004**
• < 2.0cm	28 (50.9%)	5 (16.7%)	
• 2.0 – 4.0cm	22 (40.0%)	15 (50.0%)	
• > 4.0cm	5 (9.1%)	10 (33.3%)	
Palpable Consistency			**< 0.001**
• Soft / Soft-Firm	26 (47.3%)	1 (3.3%)	
• Firm	24 (43.6%)	8 (26.7%)	
• Rubbery	3 (5.5%)	4 (13.3%)	
• Stony Hard	2 (3.6%)	17 (56.7%)	
Mobility and Fixation			**< 0.001**
• Freely Mobile / Discrete	36 (65.5%)	9 (30.0%)	
• Matted	17 (30.9%)	6 (20.0%)	
• Fixed (Skin or Fascia)	2 (3.6%)	15 (50.0%)	

Multivariable Predictive Risk Modeling

To transition from observational data to actionable clinical algorithms, variables that achieved statistical significance in univariate analysis were subjected to binary logistic regression to identify independent predictors of malignancy.

The resulting multivariable model robustly identified four key clinical parameters. **Stony hard consistency** carried the highest predictive weight (aOR = 5.92, $p < 0.001$). **Fixation to surrounding tissue** (aOR = 4.85, $p < 0.001$), **age > 50 years** (aOR = 3.65, $p = 0.002$), and **supraclavicular anatomical location** (aOR = 4.12, $p = 0.006$) all independently and significantly elevated the probability of an underlying malignant process.

Diagnostic Validity of FNAC and Molecular Testing

Fine Needle Aspiration Cytology provided a definitive cytological diagnosis in 78 of the 85 cases, yielding an overall diagnostic accuracy of 91.8%.

- **For Malignancy Detection:** FNAC correctly identified 27 of the 30 true malignancies. It achieved a Sensitivity of 90.0%, a Specificity of 96.4%, a Positive Predictive Value (PPV) of 93.1%, and a Negative Predictive Value (NPV) of 94.6%. The false negatives (n = 3) were primary lymphomas misclassified as atypical reactive hyperplasia due to a lack of architectural tissue detail.
- **For Tuberculosis (CBNAAT Integration):** While conventional ZN staining for AFB was positive in only 47.3% (n = 18/38) of cytologically confirmed tuberculous nodes, the application of CBNAAT directly on the nodal aspirate dramatically increased the detection rate, exhibiting a sensitivity of 89.4% (n = 34/38). Crucially, CBNAAT identified rifampicin resistance in 2 cases, immediately altering the prescribed pharmacological regimen prior to the initiation of empirical therapy.

- **Histopathology:** Excisional biopsy was required and executed in 14 cases, achieving a 100% diagnostic concordance with the final clinical outcome, serving as the gold standard for all equivocal FNAC presentations and suspected lymphomas.

DISCUSSION

The clinical evaluation of adult cervical lymphadenopathy stands at a critical diagnostic intersection. The findings of this standardized prospective cohort (N=85) provide a highly detailed clinical roadmap that confirms, quantifies, and contextualizes the heavy dual burden of granulomatous disease and head and neck oncology in adult medicine.

The Epidemiological Divide: Tuberculosis vs. Oncology

In this study, non-neoplastic pathologies constituted 64.7% of all cases, predominantly driven by tuberculous lymphadenitis. This mirrors the epidemiological realities of developing nations and tuberculosis-endemic zones. Tuberculous lymphadenitis is characterized by a slowly progressive, often painless enlargement of nodes, which eventually undergo central caseous necrosis, leading to capsular rupture, matting, and the formation of chronic discharging sinuses (scrofuloderma).[10] Our data corroborates that TB primarily afflicts younger adults (18-40 years) and most frequently targets the upper and middle jugular chains.

Conversely, the neoplastic burden in this cohort was alarmingly high at 35.3%. The absolute dominance of metastatic squamous cell carcinoma (91.6% of all carcinomas) within this subgroup is a direct consequence of the localized oncogenic pressures of tobacco smoking, smokeless tobacco (betel quid/gutka) mastication, and concurrent alcohol abuse. These chemical carcinogens induce sequential genetic mutations in the mucosal epithelium of the aerodigestive tract (oral cavity, pharynx, larynx), ultimately leading to invasive SCC that readily metastasizes via the rich cervical lymphatic plexus.[16]
The biphasic age distribution where nodes in a 30-year-old are statistically likely to be tuberculous, while nodes in a 60-year-old must be presumed malignant - reinforces age as a paramount clinical discriminator, validated by our multivariable model (aOR = 3.65 for age > 50).

Clinical Phenotyping and Diagnostic Algorithms

The physical palpation of a lymph node provides immense diagnostic data. The regression model utilized in this study confirms that stony hard consistency and tissue fixation are the most powerful independent clinical predictors of malignancy. The pathophysiological basis for this is sound: as metastatic epithelial cells colonize the lymph node, they induce a profound desmoplastic reaction (fibrosis), rendering the node clinically hard. As the tumor mass outgrows the nodal capsule (extracapsular spread), it physically infiltrates adjacent structures like the sternocleidomastoid muscle or the carotid sheath, manifesting clinically as fixation. [17-19]

Furthermore, the anatomical location of the node dictates the search for a primary tumor. Enlargement in the submandibular region (Level I) directs attention to the oral cavity and lips. Enlargement in the jugulodigastric area (Level II) necessitates rigorous evaluation of the tonsils and base of the tongue. The finding of isolated supraclavicular lymphadenopathy (Virchow's node) is an ominous sign, strongly correlating with metastasis via the thoracic duct from sub-diaphragmatic primary malignancies (e.g., gastric adenocarcinoma) or bronchogenic carcinomas.[20]

Pharmacological and Therapeutic Implications

The integration of rapid diagnostic modalities fundamentally alters the pharmacological trajectory for these patients.

1. Antimicrobial Stewardship in Granulomatous Disease:

Historically, tuberculous lymphadenitis was managed with empirical trials of anti-tubercular therapy (ATT) based purely on cytological evidence of granulomatous inflammation. This approach is no longer tenable. The inclusion of CBNAAT (GeneXpert) testing directly on FNAC aspirates in our protocol yielded a high sensitivity (89.4%) for Mycobacterium tuberculosis complex DNA. More importantly, from a pharmacological perspective, CBNAAT provides real-time detection of mutations in the rpoB gene, conferring resistance to Rifampicin. Identifying the two cases of rifampicin resistance in our cohort allowed for the immediate implementation of a tailored, second-line multidrug-resistant (MDR-TB) regimen. This precision prevents the clinical failure, prolonged morbidity, and epidemiological amplification associated with prescribing a standard first-line regimen (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol) to resistant strains. Furthermore, accurately identifying viral or reactive etiologies via FNAC prevents the widespread, inappropriate prescription of broad-spectrum antibiotics, preserving essential antimicrobial efficacy.[21-23]

2. Oncological Pharmacology and Staging:

For the 35.3% of patients harboring malignancies, FNAC provides a rapid, minimally invasive tissue diagnosis that dictates the staging pathway and subsequent therapeutic strategy. Metastatic SCC requires aggressive multidisciplinary management. Once cytologically confirmed, patients undergo pan-endoscopy and cross-sectional imaging

(CT/MRI/PET) to map the primary tumor. The pharmacological management of advanced HNSCC has evolved rapidly; beyond traditional cytotoxic platinum-based chemotherapy (Cisplatin, Carboplatin) and fluorouracil (5-FU), therapeutic regimens now heavily incorporate targeted biological agents. For instance, determining the exact histological subtype allows oncologists to utilize EGFR inhibitors (e.g., Cetuximab) or PD-1 immune checkpoint inhibitors (e.g., Pembrolizumab) based on the tumor's molecular profile. Delaying this diagnosis by bypassing FNAC or waiting for empirical antibiotic trials to fail drastically reduces the window of therapeutic efficacy. [24-28]

3. The Lymphoma Dilemma:
While FNAC is exceptional for diagnosing metastatic carcinomas, our data confirms its inherent limitations regarding primary lymphomas (yielding false negatives by misclassifying them as reactive hyperplasia). The pharmacological management of lymphomas (e.g., ABVD regimen for Hodgkin's, R-CHOP for Non-Hodgkin's) relies absolutely on precise WHO subtyping. Therefore, the clinical algorithm must dictate that if a patient presents with painless, rubbery, multi-level lymphadenopathy and the FNAC is inconclusive or merely "reactive," a prompt excisional biopsy is mandatory to evaluate nodal architecture and perform flow cytometry or immunohistochemistry. [24, 29-30]

Limitations of the Study
While rigorously standardized, this study possesses inherent limitations. The cohort size, while statistically adequate for identifying primary etiological trends and robust clinical predictors within the predefined parameters, may not capture extremely rare hematological or autoimmune etiologies with high precision. Additionally, the study was conducted at a tertiary referral center, which inherently introduces a referral bias; cases seen here are more likely to be complex, chronic, or neoplastic than those presenting to primary care facilities.

CONCLUSION

Adult cervical lymphadenopathy is a critical clinical entity demanding a systematic, algorithmic approach. This standardized prospective study establishes that tuberculous lymphadenitis and metastatic head and neck carcinomas constitute the vast majority of cases in the adult demographic. Careful clinical phenotyping is indispensable; advancing age (> 50 years), stony hard nodal consistency, and fixation to surrounding tissues serve as powerful, independent red flags for underlying malignancy.

Fine Needle Aspiration Cytology (FNAC) remains the cornerstone of initial investigation, offering high diagnostic accuracy with minimal morbidity. Crucially, the concurrent utilization of molecular diagnostics (CBNAAT) on cytological aspirates bridges the gap between diagnosis and advanced pharmacological management, allowing for the immediate detection of drug-resistant tuberculosis and the rapid initiation of targeted antimicrobial or oncological therapies. By adhering to structured clinical pathways, healthcare providers can minimize diagnostic delays, optimize therapeutic pharmacology, and significantly improve clinical outcomes in adult patients presenting with cervical lymph node enlargement.

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