International Journal of Health Sciences and Research
[Indexed, Peer-Reviewed Journal]
Volume 16; Issue: 4; April 2026
Website: www.ijhsr.org
Original Research Article *ISSN: 2249-9571*

Clinicopathological Presentation of Cervical Lymphadenopathy - A Cross-Sectional Study

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DOI: https://doi.org/10.52403/ijhsr.20260432

ABSTRACT

Background: Lymphadenopathy is a clinical sign characterised by abnormality in size, shape, consistency, or number of lymph nodes. The aetiology of cervical lymphadenopathy is varied and certainly different in different age groups. It is one of the most common presentations of various head and neck pathologies.
Objectives: To study and correlate the clinical presentation with pathological findings in patients with cervical lymphadenopathy. To assess the prevalence of cervical lymphadenopathy in relation to demographic data, and to report its association with various head and neck malignancies.
Methods: A cross-sectional study was conducted among 236 patients presenting with cervical lymphadenopathy at the outpatient department of Otorhinolaryngology, Hassan Institute of Medical Sciences, Hassan, from January 2021 to December 2021. Informed written consent was taken from the patients/attendees. Detailed history and clinical examination were performed. Necessary investigations include a complete blood count, ESR, chest X-ray, sputum testing, neck ultrasonography, FNAC/open biopsy, and CBNAAT. Data were analysed statistically.
Results: The majority of patients in our study were diagnosed with malignant lymphadenopathy (50.4%). Among the benign causes, reactive lymphadenitis was the most common (36.9%), followed by granulomatous lymphadenitis (12.7%). There was a 1.5:1 male-to-female ratio. The most common age groups affected were between 61 and 70 years and 51 and 60 years. Among the malignant causes, the most commonly involved primary sites were the oral cavity (13.6%), followed by the larynx (10.1%) and oropharynx (7.2%). Acid-fast bacilli and Cartridge-based nucleic acid amplification test (CBNAAT) from the lymph node aspirate were positive in 10.5% and 29.4% of the cases.
Conclusion: Cervical lymphadenopathy is the most common presentation of various head and neck pathologies. CBNAAT is a highly sensitive tissue diagnostic test that can be included in suspected cases of tubercular lymphadenitis.

Keywords: Cervical lymphadenopathy; Reactive lymphadenitis; Tubercular; Malignancy

INTRODUCTION

The term "lymphadenopathy" refers to lymph nodes that are abnormal in size, shape, or consistency, or have an increased number of lymphocytes.[1] Lymphadenitis is the pathological term that refers to lymph node swelling secondary to inflammatory processes.[2] Cervical lymphadenopathy is one of the most common presentations of various head and neck pathologies, and can occur on its own or as part of generalised lymphadenopathy.[3] The aetiology of cervical lymphadenopathy varies and may differ between age groups. The differential diagnosis includes reactive, infectious, and head and neck malignancies; lymphomas; autoimmune and iatrogenic causes; and rare disorders such as inflammatory pseudotumor (granuloma of plasma cells) and Kikuchi-Fujimoto disease.[4] The most common cause of lymphadenopathy is non-specific reactive hyperplasia (probably due to an asymptomatic inflammatory process).[5] It has been reported that the prevalence of malignancy is less than 1% in and increases to 4% in those over 40 years of age.[6,7] Metastasis to the neck with an unknown primary accounts to 3% to 5% of all head and neck cancers.[8]

With a prevalence of 43-56% in the Indian subcontinent and most Asian and African countries, peripheral tuberculous lymphadenopathy is the most frequent form of extrapulmonary tuberculosis, with cervical lymph node glands being the most commonly affected.[8] Acute lymphadenopathy (<2 weeks), subacute lymphadenopathy (2 to 6 weeks), and chronic lymphadenopathy (>6 weeks) are the three types of cervical lymphadenopathy.[9] In the paediatric population, cervical lymphadenopathy may be due to inflammation, tuberculosis, lymphoma, or exanthemous fever. In the elderly, most cases are caused by granulomatous conditions such as tuberculosis and metastasis from the oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, or thyroid. These cases are studied clinically, radiologically, and pathologically.

Understanding the prevailing conditions and various presentations of lymphadenopathy will enable us to arrive at the correct diagnosis early, preventing delays and inappropriate treatment. We planned to study the clinical presentation and correlate it with pathological findings. We also investigated the association between cervical lymphadenopathy and various head and neck malignancies.

MATERIALS & METHODS

Patients with neck swelling who presented to the Department of Otorhinolaryngology, Hassan Institute of Medical Sciences and Hospital, Hassan, between January 2021 and December 2021 were evaluated. A total of 236 patients fulfilling the inclusion criteria were enrolled in the study.

Inclusion criteria:

1) Patients of all age groups presenting to the ENT outpatient department with neck cervical lymphadenopathy.

Exclusion criteria:

1) Patients with non-lymphoid neck swelling.
2) Patients with a history of neck surgeries and previous radiotherapy.

Method of data collection:

After a detailed history and ENT examination, informed written consent was obtained from the patients/ attenders. The details have been entered into the pre-structured proforma. The patient underwent routine blood tests, including a complete blood count with ESR, liver function tests, peripheral smears, clotting and bleeding profiles, serology, X-rays, and sputum testing for AFB and CBNAAT. Neck ultrasonography and fine-needle aspiration cytology (FNAC) of the enlarged cervical lymph node were the basic investigations performed in all the study patients. Radiological investigations, such as computed tomography/ magnetic resonance

imaging (contrast-enhanced), were advised if needed (in cases of metastasis) to aid the diagnosis. An Incisional / Excisional biopsy was performed in chronic unresolved cases with treatment for definitive diagnosis, and with given ethical consideration. Lymph node aspirates or biopsy tissue were checked for the presence of Acid-fast bacilli. A cartridge-based nucleic acid amplification test (CBNAAT) was performed for patients on clinical or histological suspicion of tuberculosis. In case of unknown primary sites, endoscopies were performed.

Statistical Analysis

Statistical Package for Social Sciences [SPSS] for Windows, Version 23.0 was used to analyse the collected data. (Armonk, NY: IBM Corp) Descriptive statistics, frequency and percentages were used to describe categorical variables and the mean. Descriptive statistics include the expressions of study variables with categorical data in numerical and percentage terms.

RESULT

A total of 236 patients were evaluated in the study. Table 1 categorises the primary diagnoses into benign (49.6%) and malignant causes (50.4%). Among the benign causes, the most common is reactive lymphadenitis, 79 cases (33.5%), followed by granulomatous lymphadenitis, 27 cases (11.4%), and chronic non-specific lymphadenitis, 11 cases (4.7%). Among malignant causes, metastasis is the most prevalent overall diagnosis with 103 cases (43.6%), while lymphomas/lymphoproliferative disorders account for 16 cases (6.8%).

Table 1 depicts the distribution of various causes of cervical lymphadenopathy.

		Frequency	Per cent (%)
Benign	Reactive lymphadenitis	79	33.5
	Chronic non-specific lymphadenitis	11	4.7
	Granulomatous lymphadenitis	27	11.4
Malignant	Lymphomas/ Lymphoproliferative disorder	16	6.8
	Metastasis	103	43.6
Total		236	100

The distribution of age and gender in our study group is depicted in Table 2. The highest concentration of cases was in the 61-70 years range (48 cases, 20.3%). This is closely followed by the 51-60-year group (45 cases, 19.1%) and the 41-50-year group (41 cases, 17.4%). The lowest frequency is in patients over 71 years old (12 cases, 5.1%). And a male-to-female ratio of 1.5:1 is observed.

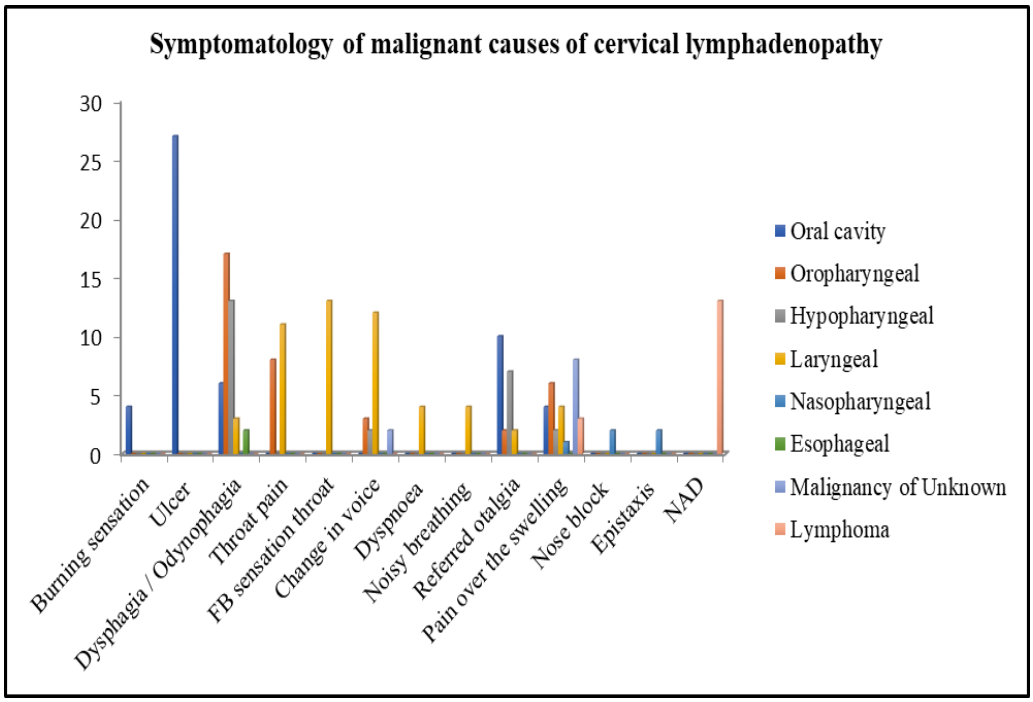
Table 2 presents the age and gender distribution across various causes of cervical lymphadenopathy.

Age (years)	Male	Female	Total	Per cent (%)
< 10	10	16	26	11.0
11- 20	8	7	15	6.4
21- 30	12	19	31	13.1
31- 40	8	10	18	7.6
41-50	30	11	41	17.4
51-60	30	15	45	19.1
61- 70	37	11	48	20.3
>71	8	4	12	5.1
Total	143	93	236	100.0

Table 3 compares the clinical symptoms associated with Benign and Malignant causes of cervical lymphadenopathy. All the patients presented with neck swelling. Pain over the swelling was significantly more common in benign cases, occurring in 48 instances compared to 22 in malignant cases. Associated symptoms such as fever and cough were reported in benign cases. Symptoms such as mouth ulcers, dysphagia/odynophagia, referred otalgia, change in voice, sore throat, nasal obstruction, epistaxis, dyspnoea, and noisy breathing were more frequently reported in malignant cases. These symptoms point to the parts involved by malignancy, as shown in Graph 1.

Table 3 depicts the symptomatology of cervical lymphadenopathy.

Symptoms	Benign	Malignant
Throat pain	8	11
Foreign body sensation in the throat	-	13
Pain over the swelling	48	22
Fever	14	-
Cough	1	-
Swelling at other sites	-	-
Burning sensation in the mouth	-	4
Ulcer in the mouth	-	27
Dysphagia/ Odynophagia	-	24
Change in voice	-	16
Difficulty/ Noisy breathing	-	4
Referred otalgia	-	19
Nose block	-	2
Epistaxis	-	2
No associated symptoms	30	13



Graph 1 Symptomatology of the malignant causes of cervical lymphadenopathy.

Table 4 details the physical characteristics and duration of the symptoms. The majority of patients experienced symptoms for 1 to 12 months (154 cases, 65.3%). Shorter durations of less than 1 month were seen in 81 cases (34.3%), and only 1 case (0.4%) had symptoms for more than 12 months. Almost all cases were unilateral (214 cases,

90.7%), with very few bilateral (3.8%) or midline (5.5%) swellings. Most swellings measured between 3 and 6 cm (146 cases, 61.9%). Swellings under 3 cm were 74 cases (31.4%), while those over 6 cm were rare (16 cases, 6.8%). Swellings were non-tender in 137 cases (58.1%) and tender in 99 cases (41.9%). The nodes were most frequently firm (112 cases, 47.4%) or hard (95 cases, 40.3%). Soft (5.9%) and rubbery (6.4%) consistencies were much less common. Nodes were mobile in 137 cases (58%) and fixed in 99 cases (42%). Involvement of a single group of lymph nodes was the overwhelming standard (193 cases, 81.8%). In 91.5% cases, the lymph nodes were discrete, and in 8.5% cases, they were matted.

Table 4 depicts symptom duration and clinical parameters.

Variable	Frequency	Per cent (%)
Duration of the symptoms		
Less than 1 month	81	34.3
1-12 months	154	65.3
More than 12months	01	0.4
Side of the swelling		
Unilateral	214	90.7
Bilateral	09	3.8
Midline	13	5.5
Size of the swelling		
Less than 3 cm	74	31.4
3 – 6 cm	146	61.9
More than 6 cm	16	6.8
Tenderness		
Absent	137	58.1
Present	99	41.9
Consistency		
Soft	14	5.9
Firm	112	47.4
Hard	95	40.3
Rubbery	15	6.4
Mobility		
Mobile	137	58
Fixed	99	42
No. of lymph nodes		
Single group	193	81.8
Two groups	34	14.4
More 2 groups	09	3.8
Nature of the lymph node		
Discrete	216	91.5
Matted	20	8.5

Table 5 maps the affected lymph node levels (IA through VI) against the specific benign or malignant diagnosis. *Level II* was the most frequently affected site across various conditions, notably in reactive lymphadenitis (37 cases, 15.7%), oral cavity malignancies (13 cases, 5.5%), and laryngeal malignancies (9 cases, 3.8%). *Level IB* was highly involved in oral cavity malignancies (24 cases, 10.2%) and reactive cases (27 cases, 11.4%). *Level V* was notably affected in granulomatous/chronic non-specific cases (14 cases, 5.9%).

Table 5 depicts the site distribution of the affected lymph nodes.

	Benign		**Malignancy**						
	Reactive	**Granulomatous/ chronic non-specific (%)**	**Oral cavity (%)**	**Oropharynx (%)**	**Hypopharynx (%)**	**Larynx (%)**	**Nasopharynx (%)**	**Malignancy of Unknown origin (%)**	**Lymphoma / lymphoproliferative disorder (%)**
IA	12 (5.1)	-	-	-	-	-	-	-	-
IB	27 (11.4)	1 (0.4)	24 10.2)	1 (0.4)	-	1 (0.4)	-	-	-
II	37 (15.7)	7 (2.9)	4 (1.7)	13 (5.5)	4 (1.7)	9 (3.8)	2 (0.8)	3 (1.3)	5 (2.1)
III	10 (4.2)	-	-	-	2 (0.8)	5 (2.1)	-	1 (0.4)	-
IV	-	-	-	-	-	-	-	1 (0.4)	-
V	-	14 (5.9)	-	-	-	5 (2.1)	-	-	4 (1.7)
VI	-	-	-	-	-	-	-	-	-
Multiple	1 (0.4)	8 (3.3)	4 (1.7)	3 (1.3)	7 (2.9)	8 (3.3)	2 (0.8)	3 (1.3)	7 (2.9)

Table 6 presents the cytological findings from the aspirated samples. Metastasis was the leading finding in 103 cases (43.6%). Benign findings included reactive lymphadenitis (79 cases, 33.5%), granulomatous lymphadenitis (27 cases, 11.4%), and non-specific lymphadenitis (11 cases, 4.7%). Lymphoproliferative lesions (unspecified) were seen in 9 cases (3.8%). In a few cases, it is specified as Non-Hodgkin Lymphoma (5 cases, 2.1%) and Hodgkin Lymphoma (2 cases, 0.9%).

Table 6 depicts the results of Fine Needle Aspiration Cytology from the enlarged lymph node.

	Frequency	Per cent (%)
Reactive lymphadenitis	79	33.5
Non-specific lymphadenitis	11	4.7
Granulomatous lymphadenitis	27	11.4
Metastasis	103	43.6
Lymphoproliferative lesions	9	3.8
Non-Hodgkin Lymphoma	5	2.1
Hodgkin Lymphoma	2	0.9
Total	236	100

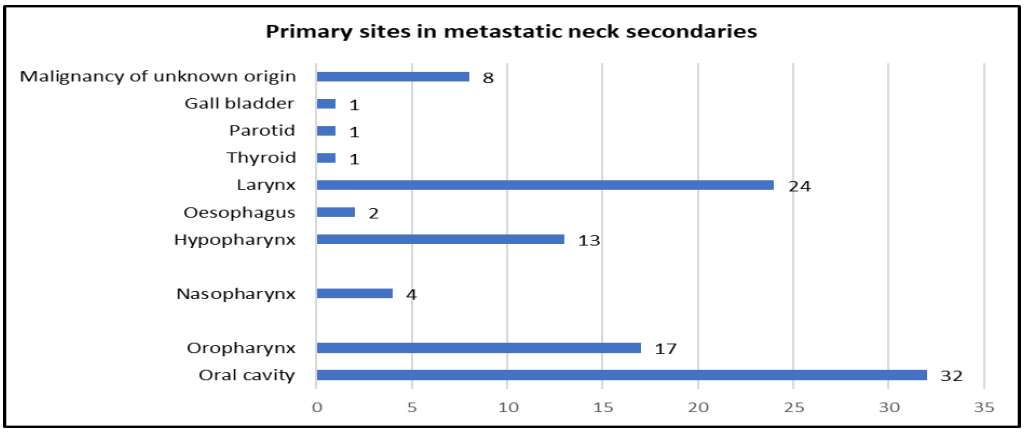
Table 7 depicts the results of Acid-Fast Bacilli (AFB) staining and CBNAAT from the lymph node aspirate.

	Acid-Fast Bacilli		CBNAAT	
	Frequency	Percent	Frequency	Percent
Negative	34	89.5	24	70.6
Positive	4	10.5	10	29.4
Total	38	100	34	100

Table 7 shows the results of 38 cases that underwent Acid-Fast Bacilli (AFB) staining. Patients with negative AFB were subjected to CBNAAT testing. Table 8 shows the comparison (cross-tabulation) between AFB staining and CBNAAT testing for tuberculosis. Of these cases, 24 (70.6%) were negative for AFB staining and CBNAAT, and 10 cases (29.4%) were positive by CBNAAT.

Table 8 presents the cross-tabulation of the percentage distribution of cases between AFB staining and CBNAAT.

			CBNAAT		Total
			NEGATIVE	POSITIVE	
AFB	NEGATIVE	Count	24	10	34
		% of Total	70.60%	29.40%	100.00%
Total		Count	24	10	34
		% of Total	70.60%	29.40%	100.00%



Graph 2 represents the distribution of primary sites in metastatic neck secondaries.

Of the 103 cases of secondary metastatic cervical deposits, the primary site was identified in 111 (93.3%), while in the remaining 8 cases (6.7%), it remained unknown, as shown in Graph 2. In our study, the most common incidence was oral cavity malignancies with 32 cases (26.9%), followed by laryngeal malignancies in 24 cases (20.2%), oropharyngeal malignancies in 17 cases (14.3%), lymphomas in 16 cases (13.5%), and hypopharyngeal malignancies in 13 cases (11%). Nasopharyngeal malignancies and oesophageal malignancies were reported in 4 (1.6%) and 2 (0.9%) cases, respectively. One case each of thyroid, parotid, and gall bladder malignancy was noted.

DISCUSSION

This discussion is based on the analysis of observations from 236 patients at Hassan Institute of Medical Sciences, Hassan, conducted during January 2021 and December 2021. The various causes of cervical lymphadenopathy were classified according to cytomorphological patterns, and their occurrence is shown in Table 1. In our research, benign causes were found in 117 (49.6%) and malignant causes in 119 (50.4%). Motiwala et al conducted a study that revealed an incidence of benign and malignant causes of 89.6% and 10.4%, respectively. [10] The distribution of age and sex in our study group is depicted in Table 2. The most affected age group was 61-70 years, with 48 cases (20.3%), followed by the 51-60 years age group with 45 cases (19.1%). The lowest incidence was observed in the age groups >71 years and 11-20 years, which does not align with most previous studies. While most earlier reports note a female preponderance. [16,17] Our study found a male-to-female ratio of 1.5:1, similar to the findings of Purohit S D et al. (1.34:1). [18]

Table 9 shows the frequency of various causes of cervical lymphadenopathy.

	Reactive/non-specific lymphadenitis (%)	Tubercular/ Granulomatous lymphadenitis (%)	Lymphomas (%)	Metastasis (%)
Maheshwari et al [11]	26 %	45 %	8 %	21 %
Gorle VK et al. [12]	16 %	51 %	10 %	8 %
Pandy, et al. [13]	14 (28%)	24 (48%)	8 (16%)	8 (16%)
Kulal et al. [14]	27 (27%)	53 (53%)	6 (6%)	14 (14%)
Kim et al. [15]	35.3%	13.9%	12.4%	25.7%
Present study	87 (36.9%)	30 (12.7%)	16 (6.8%)	103 (43.6%)

Table 9 compares the prevalent causes of cervical lymphadenopathy in the "Present study" with those in five other studies. In the present study, reactive/non-specific lymphadenitis (36.9%), tubercular/granulomatous (12.7%), lymphomas (6.8%), and metastasis (43.6%). The present study shows a notably higher metastasis rate (43.6%) compared to the other studies mentioned, which ranged from 8% to 25.7%. However, the tubercular/granulomatous rate in the present study (12.7%) is generally lower than that in several of the cited studies, which ranged up to 53%. [10,14,15,16] This may be due to the inclusion of patients from regions where tuberculosis is prevalent. This difference may be explained by the fact that our centre is a tertiary care facility specialising in head and neck cases, which leads to a higher incidence of metastases.

Duration of the symptoms and their clinical parameters are depicted in Table 4. Most of the patients (65.3%) had a symptom duration of 1 to 12 months. In 81 cases (34.3 %), lymphadenitis was reported within a month. After a year, only one case (0.4%) was reported. In this study, the primary presentation was neck swelling (100%), followed by pain at the swelling seen in 48 cases (47.5%) (Table 3). The most common constitutional symptom in patients with

tubercular lymphadenitis was fever, observed in 27 cases (61.4%), followed by pain over the swelling, seen in 12 cases (27.3%), which is consistent with Pandy et al and Kulal et al. [13,14]

The most commonly presented symptom in patients with oral cavity malignancies was an ulcerative lesion (23%). Dysphagia/odynophagia is the most often noted symptom in patients with oropharyngeal, hypopharyngeal, and oesophageal primaries, accounting for 14.5%, 11.1%, and 1.7% respectively. Foreign body sensation in the throat (11.1%), throat pain (9.4%), and hoarseness of voice (10.2%) were the symptoms of laryngeal malignancies. Referred otalgia was noted in 8.5 % of the oral cavity, 5.9 % of hypopharyngeal, 1.7% of oropharyngeal, and 1.7 % of laryngeal primaries depicted in Table 3.

In our study, observations as shown in Table 4, 214 (90.7%) had a unilateral presentation, which is comparable with the Maheshwari et al. and Pandy et al. [11,13] And 146 (61.9%) patients had neck swelling ranging between 3- 6cm, followed by < 3cm in 74 cases (31.4%) and > 6cm in 16 (6.8%) cases, which, as reported by Maheshwari et al. [11] Tender nodes were felt in 99 patients (41.9%), and fixed nodes were seen in 99 patients (42%). The disease process involved a single lymph node group in 81.8%, two groups in 14.4%, and more than two groups in 3.8%. Clinically, the involved lymph nodes were firm in 47.4%, hard in 40.3% and soft in 5.9% cases. Rubbery nodes were observed in 6.4% of the cases. Involved nodes were mobile in 137 (58%) cases and fixed in 99 (42%) cases. In 91.5% cases, the lymph nodes were discrete, and in 8.5% cases, they were matted. These findings are consistent with other studies mentioned. [11]

Among the 119 malignancies, the most frequent primary site was the oral cavity, observed in 32 cases (13.6%), followed by the larynx, observed in 24 cases (10.1%). Malignancy of unknown primary was reported in 8 cases (3.4%), as depicted in Graph 2. One case of parotid malignancy, papillary thyroid carcinoma, and gall bladder malignancy was also reported in our study.

The most commonly affected lymph node in reactive lymphadenitis was level II (15.7%), followed by IB (11.4%) and IA in 5.1%. Tubercular lymph nodes are seen involving level V in 5.9% cases, followed by level II (2.9%). Multiple tubercular lymph nodes were reported in 8 cases (3.3%) (Table 5). These findings are comparable with studies of Maheshwari et al, Baskota et al. [11,19]

The majority of the oral cavity primaries presented with level IB lymph node involvement (10.2%), followed by level II (1.7%). Oropharyngeal malignancies presented with level II lymph node enlargement in 13 cases (5.5%). Level II and level III nodes are most frequently affected by hypopharyngeal and laryngeal cancers. Nasopharyngeal malignancies and lymphomas presented with level II and level V lymph nodal enlargements (Table 5). These findings are consistent with Pandy et al., Kulal et al., and Maheshwari et al. [13,14,11]

All the patients in our study underwent FNAC of the enlarged cervical lymph node, shown in Table 6. However, most of the metastatic secondaries were diagnosed through FNAC alone; a few cases with inappropriate diagnoses underwent excisional/ incisional biopsy from the lymph node. Open biopsy and histopathological examination are considered to be the gold standard for diagnosis. Jha B.C. et al. reported 92.8% sensitivity and 88% specificity of FNAC for the diagnosis of tuberculous lymphadenitis. [20] In our study, patients with suspicion of tubercular lymphadenitis on FNAC were subjected to acid-fast bacilli (AFB) staining from the same sample, as shown in Table 7. Of the 38 samples tested for acid-fast bacilli, 4 were positive. A CBNAAT was performed on 34 negative cases. Only ten cases tested positive for tuberculosis, even though CBNAAT is a very sensitive tissue diagnostic test. This could be due to

sampling and processing errors. The cross-tabulation of the percentage distribution of cases between AFB staining and CBNAAT is depicted in Table 8 with 29.40% of cases were positive. This table clearly demonstrates that CBNAAT is more sensitive than AFB staining. CBNAAT is a more reliable and effective diagnostic tool for detecting tuberculosis in cervical lymphadenopathy.

However, with tuberculosis being more prevalent in India, the other rare causes of cervical lymphadenopathy have to be kept in mind while evaluating the patients. The majority of cases reported to our institution, a tertiary referral centre, are malignant.

CONCLUSION

Cervical lymphadenopathy is the most common presentation of various head and neck pathologies for which patients seek medical advice. Malignant causes of cervical lymphadenopathy were 50.4% in this study. The most common benign cervical lymphadenopathy was reactive lymphadenitis, followed by tuberculous lymphadenitis. Among the malignant causes, the most common was secondaries from the oral cavity, followed by laryngeal and oropharyngeal malignancies. However, globally, the highest prevalence of tuberculosis cases is seen in India. Investigations such as the CBNAAT on lymph node aspirates can be included in the routine evaluation of suspected cases. This results in early, accurate diagnosis and identification of rifampicin resistance, which significantly improves patient outcomes. In addition to refining diagnostic algorithms, further research is needed to distinguish among inflammation, benign and malignant conditions in lymphadenopathy.

Declaration by Authors

Ethical Approval: Approved
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Shreyanka M Doreswamy, Raghavendra Prasad K U, Ramitha T S. Clinicopathological presentation of cervical lymphadenopathy - a cross-sectional study. *Int J Health Sci Res.* 2026; 16(4):257-267. DOI: *https://doi.org/10.52403/ijhsr.20260432*

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