Section: Pathology

Original Research Article

CLINICOPATHOLOGICAL EVALUATION OF METASTATIC PERIPHERAL LYMPH NODES INCLUDING CARCINOMA OF UNKNOWN PRIMARY: A PROSPECTIVE STUDY FROM A TERTIARY CARE CENTRE

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ABSTRACT

Background: Metastatic peripheral lymphadenopathy is a common clinical presentation of malignancy, often necessitating comprehensive diagnostic workup to identify the primary tumour. Carcinoma of unknown primary (CUP) remains a significant diagnostic and therapeutic challenge worldwide.[3,21]
Objectives: To evaluate the cytohistological spectrum of metastatic deposits in peripheral lymph nodes, correlate clinicoradiological findings with metastatic lymphadenopathy, and establish the primary site using immunohistochemistry (IHC) where required.
Materials and Methods: This was a prospective observational study conducted over two years (March 2023 to March 2025) at Government General Hospital, Kakinada. Fifty-two patients who presented with metastatic deposits on FNAC were included. All patients underwent clinical evaluation, basic and advanced imaging, FNAC, histopathological examination (HPE), and IHC wherever required.
Results: Of 52 patients, males predominated (67.3%; M:F = 2.1:1), and the majority (48.1%) were above 60 years. Cervical lymph nodes were most commonly involved (82.7%). Head and neck region was the most frequent primary site (42.3%), followed by lung (26.9%) and thyroid (9.6%). Squamous cell carcinoma (SCC) was the dominant cytological subtype (69.2%). A 100% cytohistological correlation was achieved in 34 confirmed cases. IHC established the primary site in three cases (5.76%). CUP accounted for 7.7% of cases. Chi-square analysis showed a statistically significant association between primary site and lymph node involvement ($\chi^2 = 59.75$, $p < 0.000001$).
Conclusion: A systematic stepwise diagnostic approach integrating FNAC, imaging, histopathology, and IHC is essential for evaluating metastatic peripheral lymphadenopathy. CUP, though uncommon, requires a multidisciplinary approach and judicious use of ancillary techniques.
Keywords: Metastatic lymphadenopathy, carcinoma of unknown primary, FNAC, immunohistochemistry, peripheral lymph nodes.

INTRODUCTION

Peripheral lymphadenopathy is one of the most common clinical presentations encountered in surgical and oncological practice. Lymph nodes serve as primary sentinels of the immune system and, consequently, are frequent sites of metastatic epithelial malignancy.[1] Metastatic lymphadenopathy is a critical prognostic indicator that influences cancer staging and guides therapeutic decision-making.[2]

Among peripheral lymph nodes, the cervical group is most commonly involved, predominantly by squamous cell carcinomas arising from the upper

aerodigestive tract. Axillary lymph node involvement is closely associated with breast carcinoma, while inguinal lymph node metastases typically arise from malignancies of the lower extremities and external genitalia.[4,5] In cases with supraclavicular involvement, the primary may originate from distant sites including the lungs and gastrointestinal tract.[6]

Fine-needle aspiration cytology (FNAC) is the cornerstone of initial diagnostic evaluation in peripheral lymphadenopathy.[1,19] Histopathological examination further characterises the morphology, grade, and subtype of metastatic deposits.[18] Despite advances in imaging modalities including 18F-FDG PET-CT, a subset of cases remains classified as carcinoma of unknown primary (CUP), representing 2–5% of all cancers globally.[3,21]

This prospective study aimed to evaluate the clinicopathological profile of metastatic peripheral lymphadenopathy, with special emphasis on identifying the primary site using a systematic diagnostic approach including IHC, and to analyse the clinical and diagnostic patterns of CUP in a tertiary care setting.

2. Aims and Objectives

Aim: To evaluate metastatic deposits in peripheral lymph nodes with particular reference to unknown primary.

Objectives

1. To study the cytohistological spectrum of various metastatic deposits in lymph nodes.
2. To correlate clinicoradiological findings with metastatic lymphadenopathy.
3. To establish the primary site of malignancy with immunohistochemistry studies wherever required.

MATERIALS AND METHODS

Study design: Prospective observational study.
Duration: March 2023 to March 2025 (2 years).
Setting: Department of Pathology, Government General Hospital (GGH), Kakinada, Andhra Pradesh.
Sample size: 52 cases.

Inclusion Criteria

1. All patients presenting with metastatic peripheral lymphadenopathy as the initial presentation, diagnosed as secondary malignancy on cytology.
2. Patients who provided informed consent.

Exclusion Criteria

1. Patients diagnosed with primary lymphoma, infectious causes, or reactive lymphadenitis.
2. Intra-abdominal and intra-thoracic lymphadenopathy.
3. Metastatic peripheral lymphadenopathy in a known primary.
4. Non-cooperative patients.

FNAC was performed on all palpable peripheral lymph nodes; ultrasound-guided FNAC was used for deep-seated nodes and primary organ sampling when feasible.[1,19] Cytological smears were stained with May-Grünwald Giemsa (MGG) and Hematoxylin and Eosin (H&E).[18] Tissue biopsies were fixed in 10% formalin, processed, and stained with H&E for histopathological evaluation. IHC was performed on FFPE sections using an antibody panel including CK7, CK20, TTF-1, Napsin A, p40, CK5/6, p63, GATA3, EMA, CDX2, CEA, CA19-9, SALL4, SOX10, and PAX8 as clinically indicated.[20] Advanced imaging (CT, PET-CT, MRI, HRCT, video laryngoscopy) and serum tumour markers were used selectively. Data were analysed using descriptive statistics and chi-square test.

RESULTS

4.1 Age Distribution

The age of patients ranged from 21 to 82 years. The majority of cases (48.1%) were in the >60 years age group, followed by 41–60 years (36.5%) and 21–40 years (15.4%). No patient was below 20 years. This age predominance is consistent with the cumulative carcinogenic risk and delayed immune surveillance in the elderly.[7]

Table 1: Age Distribution

Age Group	Number of Cases (n=52)	Percentage (%)
21–40 years	8	15.4%
41–60 years	19	36.5%
>60 years	25	48.1%
Total	52	100%

4.2 Sex Distribution

Of 52 patients, 35 (67.3%) were males and 17 (32.7%) were females, with a male-to-female ratio of 2.1:1, reflecting higher prevalence of carcinogen exposure in males.[14,15]

Table 2: Sex Distribution

Sex	Number of Cases (n=52)	Percentage (%)
Male	35	67.3%
Female	17	32.7%
Total	52	100%

4.3 Site-wise Distribution of Metastatic Lymph Nodes

Cervical lymph nodes were most commonly involved (82.7%). Among cervical nodes, Level II (upper cervical) showed the highest involvement (28.8%), followed by Level I (submandibular; 25.0%) and Level V (supraclavicular/posterior cervical; 19.2%). Axillary nodes accounted for 9.6% and inguinal nodes for 7.7% of cases.[10–12]

Table 3: Site-wise Distribution of Metastatic Lymph Nodes

Lymph Node Site	Number of Cases (n=52)	Percentage (%)
Cervical – Level I (Submandibular)	13	25.0%
Cervical – Level II (Upper cervical)	15	28.8%
Cervical – Level III (Mid cervical)	3	5.8%
Cervical – Level IV (Lower cervical)	2	3.8%
Cervical – Level V (Supraclavicular + Posterior)	10	19.2%
Cervical Total	43	82.7%
Axillary	5	9.6%
Inguinal	4	7.7%
Total	52	100%

4.4 Risk Factors

Smoking was the most common risk factor (32.7%), followed by gutka/pan chewing (15.4%) and alcohol consumption (3.8%). No identifiable risk factor was present in 44.2% of patients, highlighting the multifactorial aetiology of metastatic malignancy.[3,21]

Table 4: Risk Factor Distribution

Risk Factor	Number of Cases	Percentage (%)
Smoking	17	32.7%
Gutka/Pan chewing	8	15.4%
Alcohol consumption	2	3.8%
Pesticide exposure	1	1.9%
Early menarche	1	1.9%
No identifiable risk factor	23	44.2%
Total	52	100%

4.5 Organ-wise Distribution of Primary Sites

Head and neck malignancies were the most frequent primary site (42.3%), followed by lung (26.9%), thyroid (9.6%), male genital tract (5.8%), and breast (3.8%). CUP was identified in 4 cases (7.7%).[16,17]

Table 5: Organ-wise Distribution of Primary Sites

Primary Organ Site	No. of Cases (n=52)	Percentage (%)
Head and Neck	22	42.3%
Lung	14	26.9%
Thyroid	5	9.6%
Male Genital Tract	3	5.8%
Breast	2	3.8%
Gastrointestinal Tract	1	1.9%
Foot	1	1.9%
Carcinoma of Unknown Primary (CUP)	4	7.7%

4.6 Cytological Subtypes

Squamous cell carcinoma (SCC) was the most common cytological subtype (69.2%), followed by adenocarcinoma (19.2%), papillary thyroid carcinoma (5.8%), anaplastic thyroid carcinoma (1.9%), medullary thyroid carcinoma (1.9%), and invasive breast carcinoma (1.9%).[1,14,15]

Table 6: Distribution of Cytological Subtypes

Cytological Subtype	Number of Cases	Percentage (%)
Squamous Cell Carcinoma	36	69.2%
Adenocarcinoma	10	19.2%
Papillary Thyroid Carcinoma	3	5.8%
Anaplastic Thyroid Carcinoma	1	1.9%
Medullary Thyroid Carcinoma	1	1.9%
Invasive Breast Carcinoma	1	1.9%
Total	52	100%

4.7 Cytohistological Correlation

Of the 52 cases, 34 (65.4%) underwent both cytological and histopathological evaluation. A 100% cytohistological correlation was achieved across all confirmed diagnoses, underscoring the high diagnostic accuracy of FNAC as a first-line modality.[1,13,19]

4.8 Immunohistochemistry Findings

IHC established the primary site in 3 of 52 cases (5.76%). Breast carcinoma was identified in one case (CK7+, GATA3+, EMA+; CK20−, TTF-1−), and lung carcinoma was established in two cases – one with squamous morphology (TTF-1+, p40+, CK5/6+) and one adenocarcinoma (TTF-1+, CK7+, Napsin A+).[20]

4.9 Carcinoma of Unknown Primary (CUP)

CUP accounted for 7.7% (n=4) of total cases. All four cases presented with cervical lymph node metastasis (Levels I, II, and V). Three cases showed squamous cell morphology and one showed adenocarcinoma. Despite extensive investigation including IHC, the primary site could not be identified in any of these four cases.[3,21]

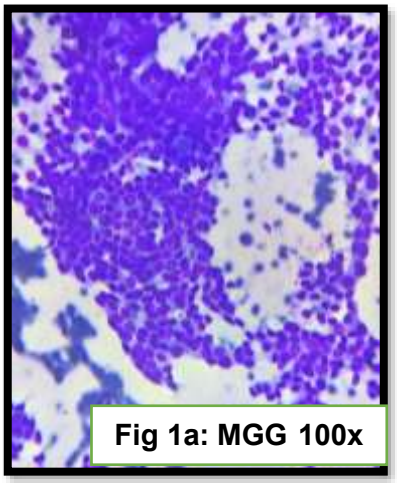
Table 7: Summary of CUP Cases

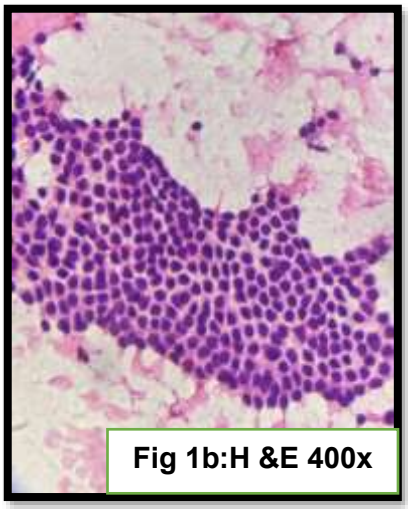
Case	Age/Sex	LN Site	Cytomorphology	IHC	Status
1	65/F	Cervical Level V	SCC	CK7+, TTF1−, P40−, GATA3−, ER−	CUP
2	65/F	Cervical Level II	Adenocarcinoma	Not done	CUP
3	30/M	Cervical Level I	SCC	Not done	CUP
4	41/F	Cervical Level II	SCC	Not done	CUP

4.10 Statistical Analysis

Chi-square analysis demonstrated a statistically significant association between the primary organ site and lymph node involvement ($\chi^2 = 59.75$, df = 14, $p < 0.000001$). Cervical node metastases were predominantly associated with head and neck, thyroid, lung, and CUP; axillary nodes with lung and breast carcinomas; and inguinal nodes with male genital tract and foot malignancies.

Fig 1: Papillary thyroid carcinoma deposits in the cervical lymph nodes





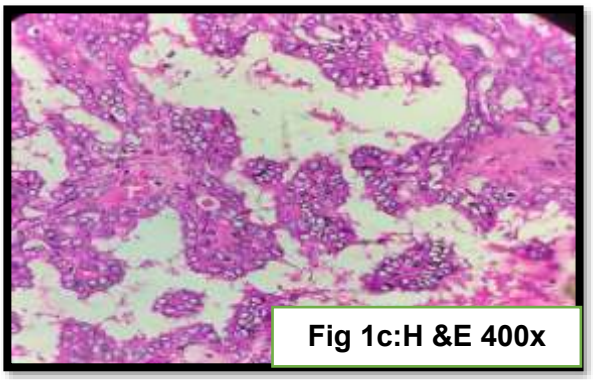


Fig 2: Medullary carcinoma deposits in cervical lymph nodes

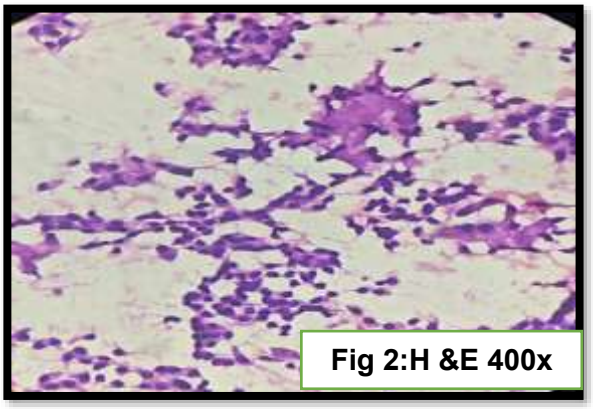
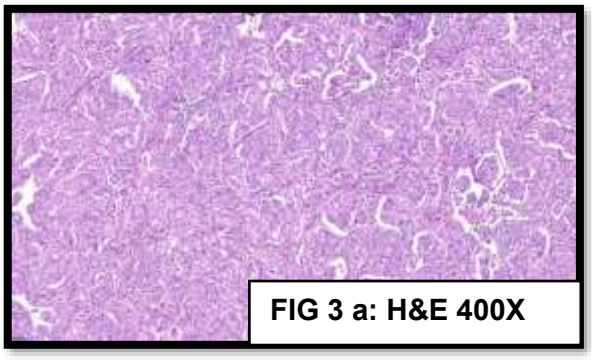


Fig 3: TTF1 positive in axillary lymph node, suggesting lung primary



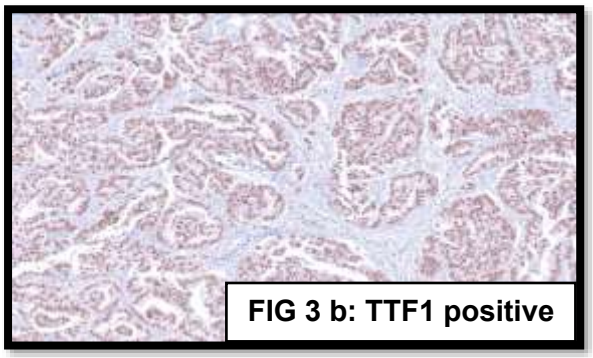


FIG 3 b: TTF1 positive

DISCUSSION

This prospective study of 52 cases of metastatic peripheral lymphadenopathy provides comprehensive clinicopathological data from a tertiary care centre in southern India. The findings are consistent with published literature and offer insights into diagnostic patterns in resource-limited settings.

Male predominance (M:F = 2.1:1) in this study aligns with reports by Sravani et al. (3.47:1),[14] Meena et al. (2.93:1),[15] and Alam et al. (2:1),[1] attributable to higher carcinogen exposure including tobacco and alcohol in males. The predominance of cases in patients over 60 years reflects cumulative risk, delayed immunity, and late presentation, consistent with findings of Ghartimagar et al. who also reported peak incidence in the >60-year age group.[7]

Cervical lymph node involvement (82.7%) was consistent with other Indian studies: Manupriya et al. reported 93.02%,[10] Chaudhary et al. 75%,[11] and Mamta et al. 77%.[12] This reflects the high burden of head and neck malignancies in tobacco-prevalent populations. Smoking was the most common risk factor (32.7%), concordant with international and Indian data linking tobacco to SCC of the upper aerodigestive tract.[3]

SCC was the predominant cytological subtype (69.2%), comparable to Meena et al. (76.3%),[15] Rathod et al. (73.4%),[8] and Sravani et al. (60.3%).[14] Adenocarcinoma (19.2%) was notably higher than in earlier studies, possibly reflecting evolving epidemiological trends including rising lung adenocarcinoma incidence. The 100% cytohistological concordance in 34 confirmed cases affirms FNAC as a reliable first-line diagnostic tool.[1,13,19]

IHC played a crucial role in establishing the primary site in three diagnostically challenging cases, using markers including TTF-1, Napsin A, GATA3, and CK7.[20] This selective, targeted approach balanced diagnostic accuracy with cost constraints. CUP was diagnosed in 7.7% of cases, comparable to Mamta et al. (6%),[12] and Sheikh and Parmar et al. (8.2%),[17] but significantly lower than Chakravarthi et al. (35.6%),[16] likely reflecting improved integration of IHC and imaging in our centre.

The statistically significant chi-square result (χ^2 = 59.75, $p < 0.000001$) confirms that lymph node distribution patterns are predictable based on primary site, which has important clinical implications for guiding targeted diagnostic investigations.[1,2]

6. Limitations

This study was conducted at a single institution with a relatively small sample size (n=52), which may limit generalisability.[16] Financial and logistical constraints prevented some patients from undergoing PET-CT and complete IHC panels.[21] Molecular profiling was beyond the study scope. Long-term follow-up data on survival and treatment outcomes were not collected.

CONCLUSION

This study affirms the importance of a structured, stepwise diagnostic approach in metastatic peripheral lymphadenopathy. FNAC achieved a 100% diagnostic yield as a first-line tool.[1,13,19] Cervical lymph nodes, SCC, and head and neck primaries dominated the clinicopathological spectrum. IHC proved indispensable in resolving diagnostically challenging cases.[20] CUP, though uncommon (7.7%), remained a significant entity, necessitating comprehensive evaluation and a multidisciplinary approach.[3,21] These findings reinforce the evolving role of pathologists as active clinical partners in oncological diagnosis and management.

Declarations

Conflict of Interest: None declared.

Funding: None.

Ethical Approval: Obtained from Institutional Ethics Committee, Rangaraya Medical College, Kakinada.

Informed Consent: Obtained from all participants.

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