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Original Research Article

Morphologic patterns of nodal reactive hyperplasia in primary organ malignancy-architectural changes and evaluation by comparison with other morphological parameters

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ABSTRACT

Background: Reactive lymph node hyperplasia can exhibit morphological patterns I to VI. This study was done to evaluate lymph node hyperplasia, lymph node reactive patterns, lymph node metastasis and correlation with tumour stage, lymph node patterns and lymph node size.
Methods: Total 454 lymph nodes were reviewed for metastases and reactivity patterns I to VI as per the World Health Organization (WHO) protocol. Association between qualitative variables was assessed by the chi-square test and Fisher's exact test, those between quantitative variables using unpaired t-test.
Results: Lymph node hyperplasia was highest in breast and commonest lymph node reactive patterns were lymphocyte predominance, germinal centre predominance, sinus histiocytosis and mixed patterns.
Conclusions: Lymph node hyperplasia and lymph node reactive patterns show organ-wise variation and need standardisation. Most common lymph node reactive patterns included lymphocyte predominance and germinal centre predominance hyperplasia. Studying lymph node reactivity may help to understand host immune reaction against the tumour and thus influence prognosis.

Keywords: Lymph node hyperplasia, Lymph node metastases

INTRODUCTION

Lymph node present adjacent to tumour-bearing organs are considered anatomic barriers to tumour spread. This imitates the host immunologic response. Lymph nodes are also the site where immune interactions between tumour antigens and lymphoid cells takes place.[1] Various studies have shown that there is certainly an active immunological interrelation between the lymphoid system and malignancy.

Lymph nodes are commonly enlarged as a result of reactive lymphadenopathy, tumour metastasis or both. Enlargement of lymph nodes may be caused by cancer cells or due to reactive hyperplasia of lymph node in response to tumour associated antigens (TAAs). In reaction to TAAs, the diverse cell population of lymph nodes react in diverse ways, giving rise to different morphological patterns (MPs).[1] TAAs, shed by tumour cells or released by cell death, are carried by lymph to the draining lymph nodes, providing non-specific and specific stimulation.[2] Morphological evaluation of lymph nodes helps in understanding the immune response.[3,4] Few studies have shown the possible correlations between patterns of Lymph node reactivity and prognosis in malignancies.[5] Analysis of morphological patterns in lymph nodes draining the tumour could reveal the immunological host-tumour association and give details on prognosis and patient survival.[3,5] Regional lymph nodes serve as effective barriers to further dissemination of tumour. Drainage of tumour cell debris or tumour antigens or both, also indicates reactive changes within

the nodes. Thus, enlargement of nodes may be caused by spread and growth of cancer cells or reactive hyperplasia of lymph nodes. Therefore, nodal enlargement in proximity to a cancer does not necessarily mean dissemination of the primary lesion.[6]

Reactive hyperplasia patterns consist of lymphocyte predominance (I), germinal centre predominance (II), sinus histiocytosis (III), vascular transformation of sinuses (IV), lymphocyte depletion (V) and granulomatous reaction (VI).[7] Inclusion of lymph node ratio (LNR) and lymph node reactive patterns in tumour reporting by pathologists may become a prognostic aid for clinicians alongside tumour stage and tumour grade.

Based on this, several investigators have done morpho-immunologic analysis of lymph nodes draining a variety of malignant tumours based on the knowledge of distribution of lymphoid cells in different classes in the nodes. In the literature, there are several studies based on these criteria, reported on carcinomas of cervix, lung, breast and larynx.[8-13] There are few studies describing lymph node reactive patterns of Oral squamous cell carcinoma.[14-17]

In this study, pattern of reaction in the involved and uninvolved lymph nodes draining malignancies was evaluated. Different patterns of hyperplasia with other morphological parameters such as size of the tumour, histological type of the tumour and histological grade of the tumour were correlated.

METHODS

This was a prospective study conducted on 454 lymph nodes isolated from 73 specimens submitted for histopathological examination in the department of pathology, LLRM Medical College, Meerut and associated SVBP Hospital, over a period of 03 years (January 2020-December 2022).

Inclusion criteria

All cases with complete resection of tumour with margins and complete resection of draining lymph nodes were included in this study.

Exclusion criteria

Post chemotherapy or radiotherapy cases or cases with tumour recurrence were excluded from the study.

After gross examination of the specimens and proper sampling, the tissues were processed by routine histological technique- paraffin embedding and sectioning at 4 µm thickness.

Histopathological diagnosis was established on routine hematoxylin and eosin (H and E) staining of the sections. Age, gender, tumour stage of primary organ malignancy, total lymph nodes dissected per case and lymph node sizes were assessed from surgical histopathology records.

The H and E-stained sections were systematically examined and the pattern of reaction in the lymph nodes was studied.

Lymph node reactive hyperplasia was categorized into following morphological patterns:[7] pattern I (lymphocyte predominance), pattern II (germinal centre predominance), pattern III (sinus histiocytosis), pattern IV (vascular transformation of sinuses), pattern V (lymphocyte depletion), pattern VI (granulomatous reaction).

Ethical approval for this study was taken from college ethical committee.

All data was recorded in MS Excel sheet. The statistical analysis was done using MS Excel and SPSS software. Association between qualitative variables was assessed by the chi-square test and Fisher's exact test.

RESULTS

There were 45, 19, 07 and 02 cases each of breast, gastrointestinal tract (GIT), genitourinary tract (GUT) and head, face, neck, thyroid (HNFT) malignancies (Table 1).

Table 1: System wise distribution.

Systems	Cases
Breast	45
GIT	19
Genitourinary	07
HNFT	02
Total	73

There was a marked female preponderance (66) over males (07) ($p<0.001$) (Table 2).

Table 2: Gender wise distribution.

Gender	Cases
Male	07
Female	66
Total	73

Table 3: Age wise distribution.

Age group(years)	Cases
0-20	0
20-40	20
40-60	47
>60	06
Total	73

Maximum number of cases were seen in 40-60 years age group (47), followed by 20-40 years age group (20) and >60 years age group (06). No case was found in 0-20 years age group (Table 3).

On histopathological examination of 358 lymph nodes, most common pattern was pattern I (lymphocyte predominance), followed by pattern II (germinal centre predominance), pattern III (sinus histiocytosis), pattern IV (vascular transformation of sinuses), pattern V (lymphocyte depletion) and pattern VI (granulomatous reaction) (Table 4).

Breast specimen yielded maximum number of reactive lymph nodes (254), which showed pattern I as the most common pattern followed by pattern II, pattern III, pattern IV and pattern V respectively. Pattern VI was not found in any case.

Table 4: Distribution of reactive patterns.

Pattern type	Cases
I	153
II	110
III	52
IV	38
V	04
VI	01
Total	358

Table 5: Distribution of lymph node reactive patterns as per primary organ involvement.

System	Lymph node reactive patterns					
	I	**II**	**III**	**IV**	**V**	**VI**
Breast (254)	122	70	33	26	03	-
GIT (65)	12	30	10	11	01	01
Genitourinary (29)	14	08	07	-	-	-
HNFT (10)	05	02	02	01	-	-
Total (358)	153	110	52	38	04	01

Table 6: Distribution of reactive and metastatic lymph node patterns as per the primary organ involvement.

System	Cases	LN	I	II	III	IV	V	VI	Mets	LNH
Breast	45	334	122	70	33	26	03	-	80	254
GIT	19	75	12	30	10	11	01	01	10	65
Genitourinary	07	32	14	08	07	-	-	-	03	29
HNFT	02	13	05	02	02	01	-	-	03	10
Total	73	454	153	110	52	38	04	01	96	358

Table 7: LNH and LNM system wise distribution.

System	Cases	LN (N)	LNH (n) (%)	Cases with mets	LNM (M) (%)	LNR
Breast	45	334	254 (70.9)	24	80 (83.3)	80/254=0.3
GIT	19	75	65 (18.1)	08	10 (10.4)	10/65=0.15
Genitourinary	07	32	29 (8.1)	02	03 (3.1)	3/29=0.10
HNFT	02	13	10 (2.7)	01	03 (3.1)	3/10=0.3
Total	73	454	358 (100)	35	96 (100)	96/358=0.26

GIT malignancies stood second in number (65) with the most common being pattern II, followed by pattern I, pattern IV, pattern III, pattern V and pattern VI respectively.

Genitourinary system with 29 lymph nodes yielded only pattern I, pattern II and pattern III.

Head, neck, face and thyroid malignancy cases with total of 10 reactive lymph nodes yielded pattern I, pattern II, pattern III and pattern IV.

A total of 73 cases were included in the study. Cases of breast were the highest in number with 45 cases, which yielded 3344 lymph nodes, 80 with metastasis and 258 with reactive pattern.

GIT malignancies stood second in number with 19 cases, which yielded 75 lymph nodes, 10 with metastasis and 65 with reactive pattern.

Genitourinary malignancies comprised of 7 cases with 32 lymph nodes retrieved, out of which 29 were reactive and 3 were metastatic.

Head, neck, face and thyroid had 2 cases with a total of 13 lymph nodes, 10 with reactive pattern and 3 with metastasis.

Out of 45 cases of breast malignancy with total of 334 lymph nodes studied, 254 with reactive pattern had LNH 70.9%, while 24 cases with metastasis had 80 lymph nodes involved with LNM 83.3%, thus yielded LNR 0.3.

Out of 19 cases of GIT malignancy with total of 75 lymph nodes, 65 with reactive pattern had LNH 18.1%, while 8 cases with metastasis had 10 lymph nodes involved with LNM 10.4%, thus yielded LNR 0.15.

Out of 7 cases of Genitourinary malignancy with total of 32 lymph nodes, 29 with reactive pattern had LNH 8.1%, while 2 cases with metastasis had 3 lymph nodes involved with LNM 3.1%, thus yielded LNR 0.10.

Out of 2 cases of HFNT malignancy with total of 13 lymph nodes, 10 with reactive pattern had LNH 2.7%, while 1 case with metastasis had 3 lymph nodes involved with LNM 3.1%, thus yielded LNR 0.3.

Thus, out of total 73 cases of malignancy with total of 454 lymph nodes, 358 with reactive pattern had LNH 100%, while 35 cases with metastasis had 96 lymph nodes involved with LNM 100%, thus yielded LNR 0.26.

DISCUSSION

Our study evaluated lymph node hyperplasia (LNH), lymph node (LN) reactive patterns and lymph node metastasis (LNM) from primary organ malignancies resected with local nodal clearance. LNH, LNM and LN patterns were studied in correlation with tumour size.

Gender and age wise distribution of cases

Akagi et al and Zeng et al reported male predominance in colorectal and gastric carcinoma, as did Chen et al in oropharyngeal malignancy.[18-20] Rubinstein et al found 88.5% male preponderance in urinary bladder malignancies.[21] In our study, we found a female preponderance. Male predominance in GIT and HFNT malignancies may reflect lifestyle-related behaviour as alcoholism, junk food, smoking and tobacco chewing.

Peak age groups of malignancy were a decade younger as compared to other studies.[18-27]

Lymph nodes harvested

LNH values were 10, 254, 65 and 29 in head, neck, breast, GIT and genitourinary respectively. Mean LNH values recommended were 10, 12, 12 and 40 in breast, GIT, genitourinary and HFNT respectively.[28-31] Techniques to further improve the yield of LNH include meticulous dissection during grossing, Intratumoral India ink injection during surgery, ex-vivo intra-arterial injection of methylene blue and chemical fat clearance using acetone and alcohol.[30-33]

Lymph node metastases

LNM values were 03, 80, 10 and 03 in head and neck, breast, GIT and genitourinary respectively in our study. Titipungul et al found mean LNM of 3.2 in breast cases, while Freneaux et al found 47.3% LNM.[23,28] Mean LNM was 1-6 in GIT cases, 0.2 and 45.5% in urinary bladder malignancies, 70 and 58% in oral cancers.[19,20,24,25,29,32]

Serial recuts, use of immunohistochemistry, one step nucleic acid amplification (OSNA) and polymerase chain reaction can further aid in detecting minute nodal metastases.[34-36]

Lymph node reactive patterns

Khetarpal et al found pattern I (0.4%), pattern II (23.7%), pattern III (12.3%) and mixed patterns (25.7%) in breast cancers.[37] Ninan et al found pattern II the most common (32) while pattern V (01) the rarest in colorectal cancers.[38] They found the most common combination patterns as II + IV, II + III and II + I (17, 14 and 9 respectively).[38] Suchitra et al found pattern I (53.49%), pattern II (31.5%) and pattern V (4.6%) in oral cancers.[25]

In our study, we found pattern I (48%), pattern II (27.5%) and pattern III (12%) in breast cancers. Pattern II was the most common (46%) in GIT cancers, pattern I (50%) in head and neck cases and (48%) in genitourinary malignancies.

Lymph node metastases and lymph node size

Markl et al found 49.5% LNM in nodes <0.5 cm and 25% in >1.0 cm of colon malignancies.[30] Burusapat et al found mean size of positive nodes as 0.3 cm in oral cancers.[39] We observed metastases in small lymph nodes upto 0.4 cm, while even lymph nodes upto 3.0 cm showed non-metastatic reactive hyperplasia.

However, we could not get any correlation of LNH, LNM and LNR with tumour stage and grade. A longitudinal follow-up study needed to confirm prognostic association, if any, for LNH and LN reactive pattern.

CONCLUSION

Nodal metastases can coexist with reactive hyperplasia. The most common lymph node reactive patterns included lymphocyte predominance and germinal centre predominance, irrespective of nodal metastases.

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