

BEYOND METASTASIS: REACTIVE LYMPH NODE CHANGES IN GASTROINTESTINAL CANCER

Histopathology

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ABSTRACT

Introduction: Regional lymph nodes act as an anatomical barrier and a site for immunological surveillance in tumor-bearing hosts. Morphological changes in these nodes—termed reactive hyperplasia—reflect the host's immune response to tumor antigens and can serve as significant prognostic markers. This study evaluates histomorphological reactive patterns in lymph nodes of primary gastrointestinal (GI) cancer to determine their correlation with metastatic status. **Methods:** A retrospective cross-sectional observational study was conducted at a tertiary healthcare center, reviewing 112 lymph nodes from 18 resected GI cancer specimens. They were valuated and categorized into patterns I–VI according to WHO protocols. **Results:** Of the 112 nodes, 54 were metastatic and 58 were non-metastatic. The most frequent reactive response was the mixed pattern, primarily characterized by sinus histiocytosis (39.2%). Significant correlations observed between germinal centre predominance pattern and metastatic cases, and lymphocytic predominance pattern and non-metastatic cases. Sinus histiocytosis coexisted across both groups and showed no statistically significant difference. **Conclusion:** Histomorphological evaluation provides critical insights into the host-tumor relationship. Germinal centre predominance signifies a humoral response associated with a higher risk of invasion, whereas lymphocytic predominance reflects cell-mediated immunity linked to a lower metastatic risk and better prognosis. Incorporating these patterns into routine pathology reports can assist surgeons in refining treatment protocols

KEYWORDS

Reactive Lymph Node Hyperplasia, GI Malignancy, Sinus Histiocytosis.

INTRODUCTION

Lymph nodes are major organs of antibody synthesis and secretion, facilitate lymphocyte expansion and also present as a site where differentiation of immunoglobulin cells take place [1]. Regional lymph nodes aid in immunological surveillance in addition to being the anatomic barrier to the systemic dissemination of tumor cells in tumor bearing hosts. The tumor itself or the structures in close proximity to the tumor such as the lymph nodes are the sites where immune response may be recognised clearly and can be assessed histologically [2].

Lymph nodes draining a tumor may enlarge either due to metastasis or reactive hyperplasia [3]. The enlargement due to hyperplasia indicates effective immunological response against cancer and could serve as a prognostic marker. The histological analysis thus may help interpret the immunological host-tumor relationship [2].

The beginning of tumor metastasis is marked by the involvement of lymph nodes. Hence, they play an important role in predicting the clinical outcome. Also, the reactive hyperplasia patterns in the lymph nodes differ in metastatic and non-metastatic cases [4].

Considering the function and characteristics of lymph nodes in tumour-bearing patients and lymph nodes being the most commonly examined tissue by histopathologists [2], this study evaluates the immune response of regional lymph nodes histologically in patients with primary gastrointestinal cancer.

There have been similar studies in various types of cancers like breast [1], uterine cervix [5], lung [6] but fewer studies focus on gastrointestinal cancer[7][4].

Hence, this study focuses on the reactive hyperplasia patterns in the metastatic and non-metastatic lymph nodes of the gastrointestinal cancer.

MATERIAL AND METHODS

A retrospective cross-sectional study was conducted in the Pathology Department of a tertiary health care centre to examine lymph nodes from primary gastrointestinal cancers recorded between July 2020 and December 2021. The study evaluated resected specimens from esophageal, gastric, small intestine, bile duct, pancreatic, and colorectal cancers, including both metastatic and non-metastatic lymph nodes. 112 lymph nodes were evaluated from 18 cases of primary gastrointestinal cancer. Lymph nodes from non-GI cancers and conditions like Inflammatory Bowel Disease were excluded.

Thin, formalin-fixed, paraffin-embedded specimen sections were stained with Haematoxylin and Eosin. Microscopic examination categorized the retrieved lymph nodes into positive and negative groups, and morphological evaluation was conducted to identify reactive patterns I–VI in accordance with WHO protocols.

These patterns included lymphocyte predominance (Pattern I), germinal centre predominance (Pattern II), sinus histiocytosis (Pattern III), vascular transformation of sinuses (Pattern IV), lymphocyte depletion (Pattern V), and granulomatous reaction (Pattern VI).

RESULTS

From 18 primary gastrointestinal cancer cases (10 males, 55.6%; 8 females, 44.4%), 112 lymph nodes were evaluated, ranging from 1 to 19 nodes per case.

Patients ranged in age from 21 to 73 years, with 10 cases aged under 60 years and 8 cases aged 60 or older. Out of the 112 lymph nodes evaluated, 54 were positive for metastasis and 58 were negative (Table 1).

The primary site of malignancy was most commonly the colon (11 cases), followed by the duodenum and stomach (2 cases each), and single cases involving the ileum, pancreas, and gallbladder.

Table 1: Distribution of Cases Based on Age, Gender and Lymph Node Involvement.

Variable	Number (n=18)	Percentage (%)
Age Group		
< 60 years	10	55.6%
≥ 60 years	8	44.4%
Age Statistics		
Range (Min-Max)	21–73	-
Mean (± SD)	55.9 (± 14.24)	-
Gender		
Male	10	55.6%
Female	8	44.4%
Lymph Nodes (n=112)		
Metastatic	54	48.2%
Non-metastatic	58	51.8%

Histomorphological analysis revealed mixed pattern as the most prevalent reactive pattern (n=44) across all age groups, followed by germinal centre predominance (n=38), lymphocytic predominance

(n=29), and a single instance of granulomatous reaction (Table 2). Notably, lymphocyte depletion and vascular transformation were absent. Mixed reactive hyperplasia was frequent, predominantly featuring a combination of germinal centre predominance and sinus histiocytosis, while the combination of lymphocytic and germinal centre predominance was the least observed.

Table 2: Reactive Hyperplasia Patterns Found in Primary Gastrointestinal Cancer.

Reactive Pattern	Number of Lymph Nodes (n=112)	Percentage (%)
Mixed Pattern	44	39.28%
Germinal Centre Predominance	38	33.92%
Lymphocytic Predominance	29	25.90%
Granulomatous Reaction	1	0.90%
Total	112	100%

Correlation of histomorphological patterns with metastatic status revealed that lymphocyte predominance was significantly more frequent in non-metastatic lymph nodes ($p < 0.0001$) (Table 3).

Conversely, germinal centre predominance was significantly higher in metastatic nodes ($p < 0.0001$). Sinus histiocytosis was the most prevalent pattern overall, appearing across both groups without a statistically significant difference. A granulomatous reaction was identified in only one non-metastatic node, precluding statistical analysis for this pattern.

No significant correlation was found between the observed reactive patterns and patient age.

Table 3: Predominant Histomorphological Reactive Patterns Observed in the Lymph Nodes of Primary Gastrointestinal Cancer.

Reactive Hyperplasia Pattern	Metastatic (n=54)	Non-Metastatic (n=58)	Total (n=112)	P-value
Lymphocytic Predominance	6	23	29	<0.0001
Germinal Centre Predominance	30	8	38	<0.0001
Mixed (Mainly Sinus Histiocytosis)	18	26	44	>0.005
Granulomatous Reaction	0	1	1	—
Total	54	58	112	—

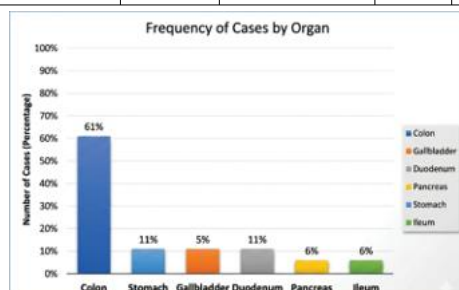


Figure 1: Distribution of the Cases According to the Organ of Malignancy

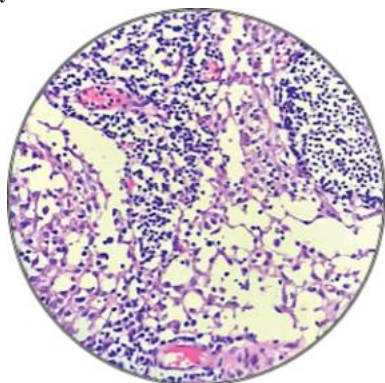


Figure 2: H&E,400x: Mixed Type of Reactive Hyperplasia in Lymph Node

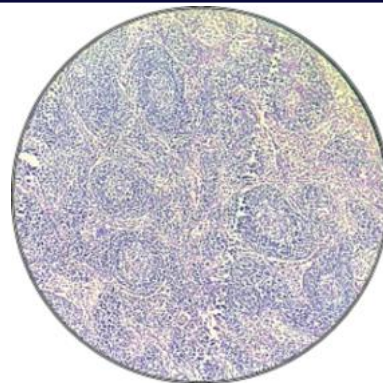


Figure 3: H&E,40x: Germinal Centre Reactive Hyperplasia in Lymph Node

DISCUSSION

Evaluating lymph node reactive patterns is vital for predicting gastrointestinal cancer prognosis and guiding therapy. Metastasis signifies a transition toward disease dissemination, yet regional nodes provide an immunological barrier through specific morphological changes. In the study on gastrointestinal cancer by Ninan et al., germinal centre predominance was found predominantly in metastatic lymph nodes [4]. Similarly in the study by Swetha et al., this pattern was observed mainly in metastatic lymph nodes (79.2%) [8]. In a study by Okura et al. on oral squamous cell carcinoma, germinal centre predominance was found to be of prognostic significance [11]. In our study, germinal centre predominance was found in total 38 lymph nodes where it is mainly identified in metastatic cases (79%) compared to non-metastatic cases (21%). Humoral immune response favors the metastatic spread through lymph nodes by inhibition of the histiocytes and the T-lymphocyte cytotoxic activity against the tumor. The reactive pattern observed in the metastatic lymph node confirms the fact that germinal centre predominance is associated with lymph node invasion and hence this theory can also be applied to gastrointestinal cancer.

In the study by Ninan et al. [4] and Swetha et al. [8], lymphocytic predominance was found predominantly in the non-metastatic lymph nodes. This is in accordance with our study where lymphocytic predominance was found in total 29 lymph nodes and is identified by markedly thickened cortex. The majority (79.3%) of which were found in non-metastatic cases compared to metastatic cases (20.7%). This pattern reflects cell-mediated immunity and is associated with better prognosis. Hence, lymphocytic predominance was the predominant pattern observed in non-metastatic lymph nodes, suggesting the fact that CMI may avert to lymph node invasion.

The study by Berlinger et al. on head and neck carcinoma mentions that both germinal centre predominance and lymphocytic predominance showed lower risk of metastasis and are associated with better prognosis [12].

Sinus histiocytosis, the major pattern found in mixed type is identified by dilatation of sinuses and hyperplasia of sinus histiocytes [1, 4, 8]. These findings were similar to McPartland et al.'s study on colon cancer [9]. It was found in total 44 lymph nodes in our study & was most commonly observed along with germinal centre predominance. However, the sinus histiocytosis pattern found in metastatic (40.9%) and non-metastatic (59.1%) did not show any statistically significant difference. Sinus histiocytosis, similar to lymphocytic predominance are also immunologic reactions of CMI. This pattern is also associated with favorable diagnosis.

Granulomatous reaction is characterized by small to large sarcoid like granulomas with a number of foreign body and Langhan's type of giant cells [14]. This type of reactive pattern is considered to be immunologic reactions of T-cell mediated immune response [13]. Ninan et al. also mentioned granulomatous reaction rarely [4]. Kheterpal et al. observed granulomatous reaction in 2 lymph nodes out of 734 lymph nodes [1]. Kennedy et al. also observed this reaction in lymph nodes of lung cancer [15]. This pattern was found the rarest (1) in our study.

A comparison of our study with other studies revealed a number of

similarities as well as dissimilarities. The differences observed can be attributed to epidemiological factors [7,10] and / or differences due to type of cancer or organ of malignancy.

CONCLUSION

This study concludes that histomorphological reactive patterns in lymph nodes provide valuable prognostic insights into gastrointestinal cancer. Lymphocytic predominance is associated with a lower risk of metastasis, reflecting protective cell-mediated immunity, while germinal centre predominance correlates with a significantly higher risk of metastatic involvement.

Incorporating these evaluations into routine pathology reports can better inform surgical and treatment protocols.

Limitations of the Study

Despite limitations like the small, unicentric sample size, these findings underscore the link between host immunity and tumor behavior.

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