Original Article

Anatomic Distribution and Histologic Subtypes of Primary Gastrointestinal Lymphomas: A Retrospective Analysis of 152 Cases

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Abstract

Background: Gastrointestinal (GI) lymphomas are a heterogeneous group of neoplasms. Studies have demonstrated a wide variation in the sites of involvement and histologic subtypes, which are independent prognostic factors. Hence, it is important to study the frequency and distribution pattern of GI lymphoma in a particular region. **Aim:** The aim of this study was to study all cases of primary GI lymphomas presented to our center for 5 years with reference to the pattern of distribution and histologic subtypes and compare our data with the literature. **Materials and Methods:** In this retrospective study, all cases of primary GI lymphomas over a period of 5 years from 2010 to 2014 were analyzed. **Results:** There were 152 cases of primary GI lymphomas. Age ranged from 3 years to 83 years. There were 133 adult patients and 19 pediatric patients. Most common site of involvement was small intestine followed by stomach, large intestine, and esophagus. Most common histologic subtype was diffuse large B-cell lymphoma (DLBCL), followed by Burkitt lymphoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma, follicular lymphoma, mantle cell lymphoma, B-cell lymphoma unclassifiable with features intermediate between DLBCL and Burkitt lymphoma, and plasmablastic lymphoma. There were five cases of T-cell non-Hodgkin lymphoma which included adult T-cell leukemia/lymphoma, anaplastic large-cell lymphoma, enteropathy-associated T-cell lymphoma, and T-lymphoblastic lymphoma. One case of Hodgkin lymphoma with predominant involvement of the large intestine and without any peripheral node involvement was also encountered. **Conclusion:** In our series, the most common site of involvement was the small intestine. This is in contrast to majority of studies where the most common site is the stomach. Similar to the other studies, DLBCL was the most common histologic subtype. Compared to other studies, there were more number of Burkitt lymphoma and lesser number of MALT lymphoma in our series.

Keywords: *Anatomic distribution, Burkitt lymphoma, diffuse large B-cell lymphoma, histologic subtypes, primary gastrointestinal lymphomas*

Introduction

The gastrointestinal tract (GIT) is the most common extranodal site involved by lymphoma.[1] Gastrointestinal (GI) lymphomas represent 1%–10% of all GI malignancies.[2] The incidence of GI lymphomas has been increasing worldwide. Primary GI lymphomas can occur in any part of the GIT. In majority of studies, stomach is the commonly affected site followed by small intestine.[3,4] Majority of GI lymphomas are non-Hodgkin lymphomas (NHLs) of B-cell origin. The most common histologic types are diffuse-large B-cell lymphoma (DLBCL) and mucosa-associated lymphoid tissue (MALT) lymphoma.[5] Few cases of T-cell lymphomas are also reported. The occurrence of Hodgkin lymphoma is extremely rare in GIT. The distribution pattern of GI lymphomas varies in different geographical regions.

Materials and Methods

In this retrospective study, all the cases of primary GI lymphomas diagnosed over a period of 5 years from January 2010 to December 2014 were analyzed. Nodal lymphomas with secondary involvement of the GIT and recurrence of previously diagnosed and treated GI lymphomas were excluded from the study. The age and sex of the patients, sites of involvement, and histologic subtypes of lymphomas were noted. The diagnosis was based on the morphological findings on hematoxylin and eosin-stained sections and the immunohistochemical profiles. The

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immunohistochemical markers used in the diagnosis and subtyping included CD45, CD20, CD79a, PAX5, CD10, CD3, CD5, CD7, CD4, CD8, CD30, BCL6, BCL2, CD38, SIgM, CD21, CD23, cyclin D1, CD138, kappa, lambda, CD34, Tdt, CD15, anaplastic lymphoma kinase (ALK), epithelial membrane antigen, cytokeratin, synaptophysin, chromogranin, and MIB-1. The subtype classification was done according to the 2008 WHO classification of tumors of hematopoietic and lymphoid tissues.[1]

Results

During the study period of 5 years (from January 2010 to December 2014), 152 cases were diagnosed as primary GI lymphomas. Twenty-four were in-house cases and 128 were referral cases from outside hospitals.

Age of the patients ranged from 3 years to 83 years and the median age was 50 years. Nineteen were pediatric patients and 133 were adults. There were 107 male patients and 45 females with a male:female of 2.4:1.

Most common site of involvement was the small intestine. There were 68 cases of small intestinal lymphomas which accounted for 44.74% of the total cases. This was followed by gastric lymphoma with 36 cases (23.68%). There were 32 cases (21.05%) of large intestinal lymphomas, 13 cases (8.55%) of ileocecal lymphomas, and 3 cases (1.97%) of esophageal lymphomas [Table 1].

DLBCL was the most common histologic variant. There were 82 cases of DLBCL (53.95% of total cases). In all the anatomical sites, DLBCL was the predominating subtype [Table 1].

There were 29 cases (19.08% of total cases) of Burkitt lymphoma. Of these 29 cases, 21 cases occurred in the ileum and ileocecal region. Seventeen cases were in the age group of 3–10 years with a striking male predominance (15 male and 2 female patients).

There were 17 cases of MALT lymphoma which formed 11.18% of the total cases. Predominant site of involvement was the stomach followed by small intestine, large intestine, and ileocecal region.

Of the nine cases of follicular lymphoma, seven cases occurred in the small intestine. One case each involved the large intestine and the ileocecal region. Majority of the cases (six cases) were Grade 3 follicular lymphomas.

Four cases of primary mantle cell lymphomas including two cases of blastoid mantle cell lymphomas were reported. Two cases involved the large intestine, one case each in the small intestine and in the stomach.

Three cases were classified as B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma. All the three cases were in the small intestine.

Table 1: Site distribution and histological subtypes of gastrointestinal lymphoma

Site	*n* (%)	Histological subtype and number of cases
Esophagus	3 (1.97)	DLBCL - 2
		Plasmablastic lymphoma - 1
Stomach	36 (23.68)	DLBCL - 21
		Burkitt lymphoma - 4
		MALT lymphoma - 8
		Blastoid mantle - 1
		ALCL - 1
		T-lymphoblastic lymphoma - 1
Small intestine	68 (44.74)	DLBCL - 37
		Burkitt lymphoma - 13
		MALT lymphoma - 5
		Follicular Lymphoma - 7
		B-cell lymphoma, unclassifiable, with features intermediate DLBCL and Burkitt lymphoma - 3
		EATL - 1
		Mantle cell lymphoma - 1
		Plasmablastic lymphoma - 1
Ileocecum	13 (8.55)	Burkitt lymphoma - 8
		DLBCL - 2
		MALT lymphoma - 1
		Follicular lymphoma - 1
		ATLL - 1
Large intestine	32 (21.05)	DLBCL - 20
		Burkitt lymphoma - 4
		MALT lymphoma - 3
		Follicular lymphoma - 1
		Mantle cell lymphoma - 1
		Blastoid mantle - 1
		ATLL - 1
		Hodgkin lymphoma - 1

DLBCL: Diffuse large B-cell lymphoma, MALT: Mucosa-associated lymphoid tissue, ALCL: Anaplastic large cell lymphoma, EATL: Enteropathy-associated T-cell lymphoma, ATLL: Adult T-cell leukemia/lymphoma

There were two cases of plasmablastic lymphoma, one in the esophagus and one in the small intestine.

Five cases of T-cell lymphomas were encountered which constituted 3.29% of the cases and included adult T-cell leukemia/lymphoma (ATLL) (two cases), anaplastic large cell lymphoma (ALCL) (one case), enteropathy-associated T-cell lymphoma (EATL) (one case), and T-lymphoblastic lymphoma (one case).

There was one case of primary Hodgkin lymphoma involving the large intestine with the main bulk of disease in the large intestine with minimal involvement in the pericolic nodes and no evidence of other nodal involvement.

During the study, we encountered three cases with synchronous occurrence of lymphomas and nonlymphoid malignancies. This included one case of MALT lymphoma and adenocarcinoma of stomach, one case of DLBCL of stomach and neuroendocrine tumor of duodenum, and another case of DLBCL of intestine and nonsmall cell carcinoma of lung.

Discussion

Gastrointestinal lymphomas are a heterogeneous group of neoplasms and constitute 10%–15% of all NHLs.[6] In 1961, Dawson *et al*. defined primary GI lymphomas as a tumor that predominantly involves the GIT with lymph node involvement confined to the drainage area of the primary tumor site. According to these authors, there should not be any palpable lymph nodes or involvement of liver or spleen. There should be normal chest radiograph and normal peripheral white cells.[7] Later, in 1978, Lewin *et al*. defined primary GI lymphomas as those in which the involvement of alimentary tract predominates or those with symptoms of GIT involvement on presentation.[8]

The amount and nature of lymphoid tissue vary in different parts of intestine. The risk factors involved in the development of GI lymphoma include *Helicobacter pylori* infection, human immunodeficiency virus, *Campylobacter jejuni*, Epstein–Barr virus, hepatitis B virus, human T-cell lymphotropic virus-1 (HTLV-1), celiac disease, inflammatory bowel disease, and immunosuppression.[9,10]

The histological subtypes of GI lymphomas vary according to the normal lymphoid distribution and according to the etiological factors. Clinically, GI lymphomas are indistinguishable from other benign and malignant conditions. Hence, biopsy is essential for a definite diagnosis. On histopathologic examination, low-grade lymphomas should be differentiated from reactive lymphoid infiltrates and high-grade lymphomas from nonlymphoid malignancies. Certain histological subtypes have been noted to have a relative predilection site. For example, MALT lymphoma occurs more commonly in stomach, mantle cell lymphoma in terminal ileum, jejunum, and colon, EATL in jejunum, and follicular lymphoma in duodenum.[11]

Distribution pattern

Primary lymphomas are very rare in the esophagus and constitute <1% of all GI lymphomas. Endoscopic findings of ulcers, plaques, polypoidal or circumferential lesions can mimic carcinoma. Histopathologic examination is essential in making the diagnosis. Esophageal lymphomas usually occur as a result of secondary involvement from cervical or mediastinal lymph nodes or direct extension from gastric lymphoma. Nonlymphoid malignancy and secondary involvement of lymphomas should be excluded before making a diagnosis of primary esophageal lymphoma.[12-14] In our series, there were three cases (1.97%) of primary esophageal lymphomas, two cases of DLBCL, and one case of plasmablastic lymphoma.

Literature search shows stomach as the most frequent site of involvement of GI lymphomas in majority of studies ranging from 38.5% to 75% [Table 2].[15-18] In stomach, B-lymphocytes and plasma cells are absent and a few CD8 positive T-cells can be seen in intraepithelial locations and CD4 positive T-cells in the lamina propria. Reactive lymphoid follicles are seen in chronic gastritis. Chronic gastritis associated with *H. pylori* infection is a precursor for the development of MALT lymphoma.[12,14] Lymphoepithelial lesions, dense ill-defined infiltrate of monotonous B-cells extending away from lymphoid follicles, and cytological atypia favor a neoplastic process. In our series, stomach was the second most common site of involvement. There were 36 cases of primary gastric lymphomas which constituted 23.6% of all GI lymphomas. In contrast to majority of studies where MALT lymphoma is the most common subtype of gastric lymphoma, DLBCL was the predominant subtype in our study and constituted 21 cases (58.3% of all primary gastric lymphomas).[14-17] There were eight cases of MALT lymphoma, four cases of Burkitt lymphoma, one case each of blastoid mantle cell lymphoma, ALCL, and T-lymphoblastic lymphoma.

Small intestine was the most common site of involvement by primary GI lymphoma in our study. This is in contrast to the majority of published studies.[14-17] In the intestine, there are large amount of lymphoid tissue in the mucosa and submucosa which contain both B- and T-cells and elicit adaptive immune response against the mucosal antigens.[12-14] In our study, the subtype distribution of small intestinal lymphomas was more diverse. In adults, DLBCL was the most common subtype whereas in children, Burkitt lymphoma was the predominant type. Others included follicular lymphoma, MALT lymphoma, B-cell lymphoma

Table 2: Site distribution of gastrointestinal lymphoma and comparison with literature

Author	Country	Number of cases	Esophagus (%)	Stomach (%)	Small intestine (%)	Ileocecum (%)	Large intestine (%)	Multiple sites (%)
Ding *et al*.[15]	China	1010	4 (0.4)	521 (51.6)	173 (17.1)	92 (9.1)	186 (18.4)	34 (3.4)
Shirsat and Vaiphei[16]	India	81	1 (1.23)	40 (49.38)	24 (29.63)	3 (3.7)	4 (4.94)	9 (11.11)
Warrick *et al*.[17]	USA	216	3 (1.39)	97 (44.91)	57 (26.39)	19 (8.8)	40 (18.52)	-
Arora *et al*.[14]	India	336	0	180 (53.57)	79 (23.51)	34 (10.12)	34 (10.12)	9 (2.68)
Current study	India	152	3 (1.97)	36 (23.68)	68 (44.74)	13 (8.55)	32 (21.05)	-

unclassifiable with features intermediate between DLBCL and Burkitt lymphoma, EATL, mantle cell lymphoma, and plasmablastic lymphoma.

Ileocecal region was defined as the area from the terminal of ileum to the cecum. The ambiguity of anatomical classification of this site resulted in different frequencies of small intestinal and large intestinal lymphomas. In this study, 13 cases (8.55%) were in the ileocecal region. Majority were Burkitt lymphoma. Others included DLBCL, MALT lymphoma, follicular lymphoma, and ATLL.

Primary colorectal lymphomas account for 0.2%–0.6% of all large intestinal malignancies. Inflammatory bowel disease and immunosuppression are the risk factors for the development of primary colorectal lymphomas. In our series, there were 32 cases of colorectal lymphomas. DLBCL was the predominant subtype with twenty cases. The subtype distribution was diverse and included Burkitt lymphoma, MALT lymphoma, follicular lymphoma, mantle cell lymphoma including blastoid variant, ATLL, and Hodgkin lymphoma.

Histologic subtypes

DLBCL is the most common subtype of primary GI lymphoma in majority of the studies.[14-21] In our study also, DLBCL was the most common histological subtype and accounted for 53.95% of total cases [Table 3]. In all the anatomical sites, DLBCL was the most common subtype. DLBCL with signet ring-like morphology and CD5 positive DLBCL were encountered in the study period.

In contrast to the majority of studies, our study showed increased number of Burkitt lymphoma cases.[14-17] Common sites affected by Burkitt lymphoma were the small intestine and the ileocecal region. Majority of the cases occurred in the pediatric age group.

The incidence of MALT lymphoma was less compared to other studies. In cases where there was difficulty in distinguishing reactive lymphoid infiltrate and MALT lymphoma, features such as cellular atypia, lymphoepithelial lesions, and sheeting of B-cells with CD20 staining helped in arriving at definite diagnosis. The distinction between MALT lymphoma with extensive plasmacytic differentiation and plasmacytoma was challenging. Extensive search for the presence of a small lymphoid cell infiltrate along with CD20 positivity and absence of other parameters of myeloma helped in the differentiation.

Of the nine cases of follicular lymphoma, seven cases occurred in the small intestine. Six cases were Grade 3 follicular lymphomas.

We encountered four cases of mantle cell lymphoma which included two cases of blastoid variant. Common presentation of mantle cell lymphoma was as polypoidal masses. The use of CD5 in the first-line immunopanel helped in the identification of blastoid mantle cell lymphoma.

Three cases were diagnosed as B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma. All the three cases occurred in the small intestine and showed a high MIB-1 labeling index.

Two cases were diagnosed as plasmablastic lymphoma. One case was in the esophagus and the other was in the small intestine. Both these cases occurred in immunocompetent people.

The occurrence of T-cell lymphomas is rare in the GIT.[22,23] In our study, there were five cases of T-cell lymphomas which accounted for 3.29% of cases. It included ATLL, ALCL, EATL, and T-lymphoblastic lymphoma. There were two cases of ATLL, one case involving the ileocecum and the other involving the large intestine. The neoplastic cells showed positivity for CD3 and CD5 with downregulation of CD7. The cells were also positive for CD25. The diagnosis was confirmed by serum HTLV-1 estimation. One case of ALCL involving the stomach was encountered where the neoplastic cells were brightly positive for CD30 and ALK, weakly positive for CD45 and CD3, and were negative for B-cell markers. One case of EATL involving the ileum was encountered where the neoplastic cells were CD3 and CD7 positive and CD5 negative. There was one case of T-lymphoblastic lymphoma involving the stomach in an adult patient. The neoplastic cells were positive for CD3, CD5, and Tdt and were negative for CD34, CD10, CD20, CD33, MPO, and BCL6. Blood smear and bone marrow were within normal limits.

One case of classical Hodgkin lymphoma involving the large intestine without any evidence of peripheral node involvement was noted in the study period. Microscopy showed large mono- and bi-nucleate cells with prominent

Table 3: Histological subtypes of gastrointestinal lymphoma and comparison with literature

Author	Country	Number of cases	DLBCL (%)	MALT lymphoma (%)	Burkitt lymphoma (%)	T-cell lymphoma (%)
Ding *et al*.[15]	China	1010	580 (57.43)	209 (20.7)	34 (3.37)	130 (12.87)
Shirsat and Vaiphei[16]	India	81	21 (25.93)	48 (59.26)	0	9 (11.11)
Warrick *et al*.[17]	USA	216	87 (40.28)	55 (25.46)	10 (4.63)	10 (4.63)
Arora *et al*.[14]	India	336	222 (66.71)	34 (10.12)	35 (10.48)	11 (3.27)
Current study	India	152	82 (53.95)	17 (11.18)	29 (19.08)	5 (3.29)

DLBCL: Diffuse large B-cell lymphoma, MALT: Mucosa-associated lymphoid tissue

eosinophilic nucleoli in a polymorphous background of small lymphocytes, plasma cells, histiocytes, eosinophils, and neutrophils. The large atypical cells were CD20 negative, CD30 positive, PAX5 positive, and CD15 negative. Primary involvement of GIT is very rare in Hodgkin lymphoma. Secondary involvement should always be excluded by detailed clinical and radiological evaluation.

Synchronous cases of lymphoma and nonlymphoid malignancies are well described. There was one case of synchronous MALT lymphoma and adenocarcinoma of the stomach. Recently, there is a worldwide increased rate of detection of the cooccurrence of these two tumors. Various theories have been put forward to explain this occurrence. One theory is that one preexisting tumor provokes the other. Another theory is that the two tumors arise independently as a result of the same carcinogenic action.[24] It is suggested that *H. pylori* might play an important role in the development of both lymphoma and carcinoma. We had one synchronous case of DLBCL of the stomach and neuroendocrine tumor of the duodenum. Another case showed synchronous occurrence of DLBCL intestine and nonsmall cell lung cancer.

Conclusion

This retrospective study from a single institution highlights the anatomic distribution and histologic subtypes of primary GI lymphoma in a southern state of India. In this study, DLBCL was the most common histologic subtype in all the anatomic sites. This finding is in concordance with other studies. The incidence of MALT lymphoma was low and there was a strikingly high incidence of Burkitt lymphoma. In contrast to other studies, small intestine was the most common site of involvement of GI lymphoma in our study. These findings highlight the geographic variation in the occurrence of GI lymphoma in our area.

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Conflicts of interest

There are no conflicts of interest.

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