ORIGINAL RESEARCH PAPER

Pathology

HISTOPATHOLOGICAL ANALYSIS OF GASTROINTESTINAL LYMPHOMAS AT A TERTIARY CARE CENTRE WITH REVIEW OF LITERATURE

KEY WORDS:
Gastrointestinal tract lymphomas, Non-Hodgkin lymphoma, Diffuse large B cell lymphoma.

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ABSTRACT

BACKGROUND: Primary gastrointestinal lymphoma is the most common extranodal non-Hodgkin lymphoma representing a wide spectrum of disease . It constitutes 10–15% of all non-Hodgkin's lymphoma and about 30–40% of extra-nodal lymphomas. The incidence of GI lymphomas varies across the globe . It can involve any site from the esophagus to the anal canal.
AIM: This study aims to analyse the clinical features , anatomic distribution, histological subtypes and sites of all GIT lymphomas presenting to a tertiary care centre .
STUDY DESIGN : Descriptive study. **MATERIALS AND METHODS:** The histological material in 21 patients over a period of 8 years (2011–2019), with a histopathological diagnosis of lymphoma involving the GIT was analyzed retrospectively. All lymphomas were reclassified according to the World Health Organization 2019 classification.
RESULTS: There were 21 cases of GI lymphomas. 11 males and 10 females with a male to female ratio of 1.1:1. Predominantly middle aged and elderly range from 41-79years is involved. The commonest clinical presentation was abdominal discomfort and abdominal pain. The commonest site involved is ileum and Diffuse large B cell lymphoma is the commonest subtype (71.42%). Only one case of T cell lymphoma was recognized.

INTRODUCTION

The most common site of extra nodal lymphoma is gastrointestinal tract. Gastrointestinal (GI) lymphomas account for 30-40% of extra nodal lymphomas[1]. Majority of them are Non-Hodgkin lymphomas (NHL) of B cell origin. This includes Mucosa Associate Lymphoid Tissue (MALT) lymphoma, immunoproliferative small intestinal disease, mantle cell lymphoma (MCL) , Burkitt lymphoma, Diffuse large B cell lymphoma (DLBCL) , B- cell lymphoma unclassifiable and follicular lymphoma (FL). DLBCL is the commonest one amongst them[2]. Tcell lymphomas also account for a minor percentage.

GI lymphomas can involve any site from the esophagus to the anal canal. According to literature, the most common observed site in western countries, is stomach (approximately 35–75%), followed by the small intestine (30%) and large intestine (10%). However, it can vary according to the geographical regions[3]. The possible risk factors for GI lymphoma include - Helicobacter pylori infection, immunosuppression after organ transplantation, coeliac disease, ulcerative colitis and human immunodeficiency virus infection[4].

In this descriptive study we have analyzed the clinical features, anatomic distribution and histological types of GI lymphomas at our centre and reviewed the literature.

MATERIALS &METHODS

This is a descriptive study carried out in the Department of Pathology, Amala Institute of Medical Sciences, Thrissur, Kerala, India over a period of 8 years from 2011 to 2019. Here, the clinical presentation, anatomic distribution and histological types of GI lymphoma cases which we received at our centre during this time period were analyzed. A total of 21 cases were analyzed. Study material included small biopsy specimens as well as resections. Patients registered in the hospital and referral cases were included in this study.

All specimens were processed in 10%neutral buffered formalin and 5micron paraffin sections stained with hematoxylin and eosin were studied. A morphological diagnosis of lymphoma was made and was subtyped into B cell and T cell lymphomas. Immunohistochemistry (IHC) was done using appropriate external and internal controls. Conventional avidin–biotin peroxidase technique, with chromogen diaminobenzidine (DAB) was used. Pretreatment was done by heating in a pressure cooker in 0.01 M citrate buffer (pH 6.0)/1 mm EDTA buffer (pH 8.0). A single B cell marker and T cell marker was used to categorize the lymphoma into the 2 subtypes. The B cell marker used was CD20 and the T cell marker used was CD3. Other markers used, include LCA,CD5,CD10, BCL-2,BCL 6, cyclin D1, CD 15, CD 30, c-Myc and CD 23. Ki 67 was used to assess the proliferation index. All the cases were reviewed and re-classified based on morphological and immunophenotypic features. All the relevant clinical and investigation details were retrieved from the hospital archives.

RESULTS

A total of 21 cases were reported over the study period of 8 years at the Department of Pathology at Amala Institute of Medical Sciences were analyzed. It included 11 males and 10 females, with a male to female ratio of 1.1:1. Lymphomas are predominantly seen in the middle aged and elderly. Age ranged from 41 to 79 years with a mean age of 60.6 years.

The most common clinical presentations were abdominal discomfort and pain. Other symptoms included loss of appetite, bleeding per rectum, altered bowel habits and loss of weight. Although any site in the GI tract can be involved, the most common site of involvement in this study is ileum with a total of 4 cases. Other sites of involvement include ileo-caecal junction, large intestine, jejunum and stomach (Table 1).

Table 1: Anatomical distribution of GI lymphomas in this study

SITE	CASES
Ileum	4
Ileocaecal junction	3
Jejunum	3
Stomach	2
Ascending colon	3
Caecum	3
Rest of the colon	3
TOTAL	**21**

All the cases analyzed in this study were Non-Hodgkin Lymphoma. On morphological analysis, based on histopathology alone we divided the lymphomas into 16 high grade lymphomas,1 intermediate grade lymphoma and 4 low grade lymphomas. B and T cell IHC markers were used and that confirmed that 20 cases were B cell lymphomas and there was one case of T cell lymphoma. Other IHC markers - LCA, CD5 , CD10 , Bcl-2 , Bcl-6, Cyclin D1,CD 15,CD 30, c-Myc , CD 23 and Ki 67 were used accordingly .The most commonly observed lymphoma was high grade B cell lymphoma –diffuse type(15 cases) and it was mainly observed in the ileum. There was one case of intermediate grade lymphoma – mantle cell type. The low grade cases included 3 cases of follicular lymphoma and one case of marginal zone B cell lymphoma (MALT).

DISCUSSION

Primary GI lymphomas are relatively rare compared to secondary involvement of GI tract in nodal lymphomas. In this study over a period of 8 years, we retrieved and analyzed 21 cases of primary GI lymphomas at our centre. The incidence calculated was almost comparable in both the genders with a very minimal male preponderance. Studies by Lewis et al showed similar gender distribution[8]. In our study majority of the patients belonged to the middle to elderly age group. This is comparable with the study done by Arora et al[6]. The most common site involved is ileum followed by ileo-caecal region. This is consistent with the observations of Li et al[7] Wang etal[8]and Kohno et al[9]. But one Indian study from CMC Vellore showed stomach as the most commonest site[6].While study by Koch P et al revealed small intestine and ileo-caecal region as the commonest sites[10].

Diffuse large B cell lymphoma is the most common histological type in our study. This is in concordance with the study done on Indian population by Arora et al[6]. Rest of the cases, were intermediate grade lymphoma and low grade lymphomas. One case of T cell lymphoma of colon is also noted. (Table 2).

Table 2: Comparison of the present study with other Indian studies.

Study	Total No of cases	M:F	Age	Histopathology	Stomach	Small intestine	Large intestine
Present study	21	1.1:1	60.6	DLBCL	2	10	9
Arora et al[6]	336	4.30:1	45	DLBCL	192	79	68
Raina et al[11]	77	2.2:1	32	Diffuse large cell	36	28	13
Chandran et al[12]	49	2.8:1	30	High grade lymphoblastic lymphoma	14	31	

Diffuse Large B Cell Lymphoma [6,13]

It is the most common type of lymphoma of the GI tract in literature accounting to 55-69%. This is comparable to our result of 71.42% of DLBCL. It can involve any part of the digestive tract but most commonly involves the stomach and ileo-caecal region. In this study majority of DLBCLs involved the ileum , followed by ileo-caecum. Patients frequently present with abdominal pain , discomfort or symptoms and signs related to bleeding , obstruction or perforation. B symptoms may be present. In the GI tract , they can present as solitary infiltrative fleshy tumor mass with ulceration of mucosa. DLBCL cases in this study showed similar gross appearance(Figure 1). It usually shows transmural infiltration. Microscopy shows sheets of large cells which are positive for CD19,CD20 ,CD79a ,PAX 5 and a high Ki67 of >40%(Figure2a-d). Hans algorithm can be used to divide it into germinal centre B cell type and activated B cell type. (Figure 3). However ,this has not been applied in this study owing to the limited number of IHC markers.

Figure 1: Segment of large intestine showing a large intraluminal polypoidal tan brown fleshy homogenous mass:

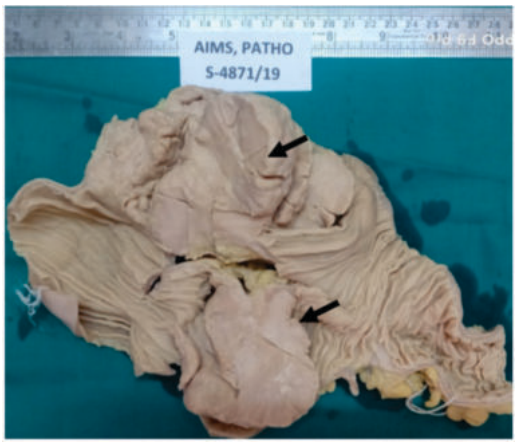


Figure 2a: Monotonous population of medium to large sized lymphoid cells in the large intestinal mucosa.H&E-100X

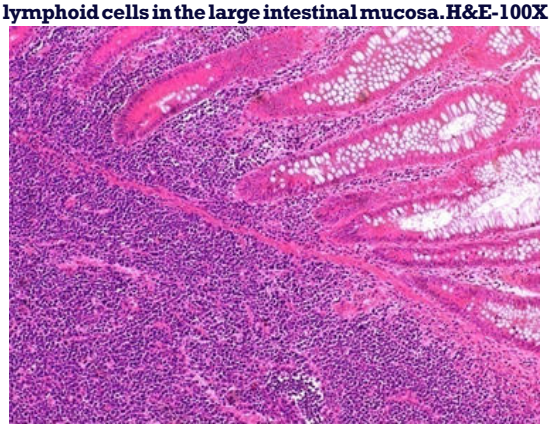


Figure 2b :Cells are medium to large sized with scanty cytoplasm, large nucleus, coarse chromatin and prominent nucleoli,H&E-400X

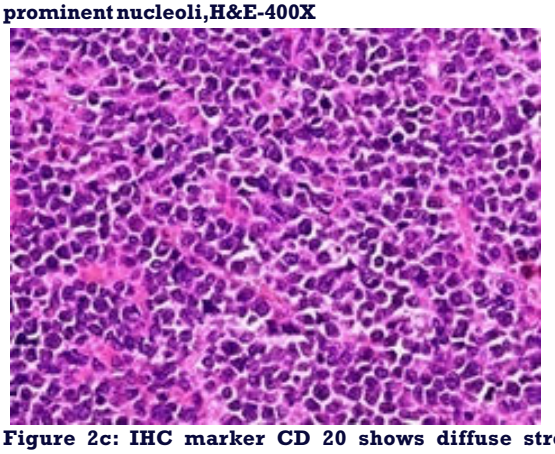


Figure 2c: IHC marker CD 20 shows diffuse strong positivity 100x

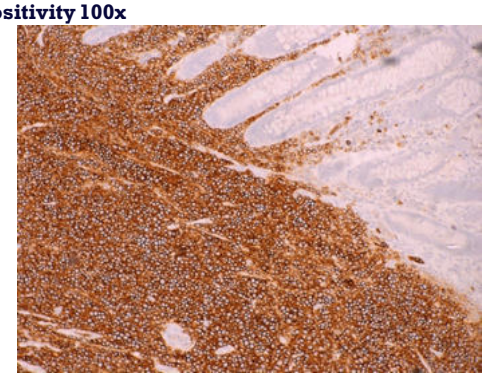


Figure 2d:High Ki 67 index ,400X

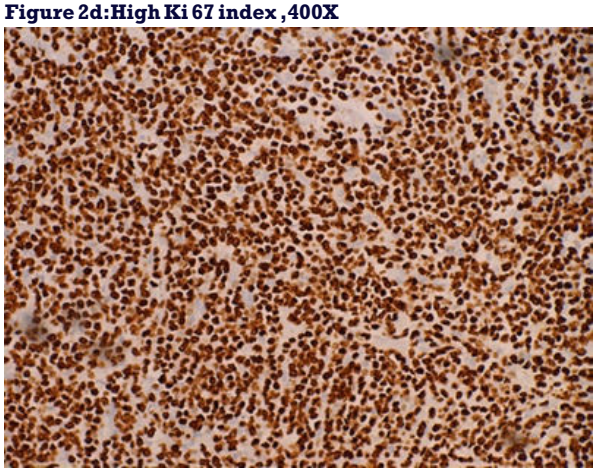
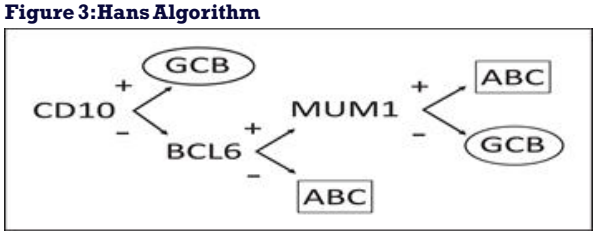


Figure 3:Hans Algorithm



Follicular lymphoma[6,13]

This study has 3 cases of follicular lymphoma in the elderly age group , who presented with abdominal discomfort. Follicular lymphoma is a malignant lymphoid neoplasm of the follicular centre B cells typically showing follicular architecture. Primary digestive tract follicular lymphoma occurs most often in the small and large intestine. All three cases in this study involved the small bowel. Usual symptoms include abdominal discomfort,obstruction or intestinal bleeding. Follicular lymphomas constitutes < 4% of the primary GI lymphomas. Mean patient age is 50 years. Microscopy shows transmural infiltration of the organ wall by centroblasts and centrocytes. Lymphomatous polyposis may also be seen. Diagnosis requires recognition of at least partly follicular proliferation of centroblasts and centrocytes. Most cases are Grade I/II. FL cells express B cell markers,CD19, CD20 and are positive for CD10, BCL-6 and BCL-2(Figure 4a-c). Rarely CD5 is positive. Follicular dendritic cell meshworks are well preserved unlike in duodenal FL. Hallmark is of follicular lymphoma is t(11;14) which results in Bcl-2 and IGH gene fusion and is detected in 90% of cases. 2 cases of follicular lymphomas in this study belonged to Grade II and one case was Grade I.

Figure 4a: Segment of small intestine showing thickened wall with homogenous fleshy appearance .

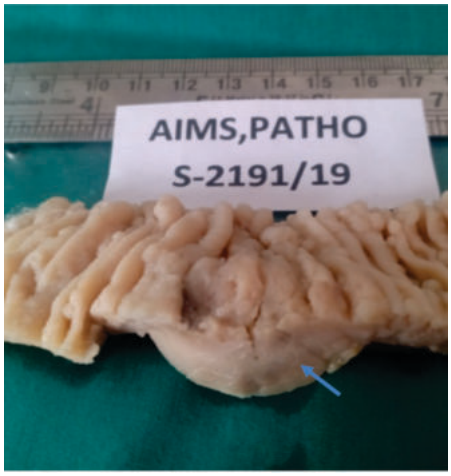


Figure 4b: Small to medium sized lymphoid cells arranged in follicular pattern separated. H&E 100 X,

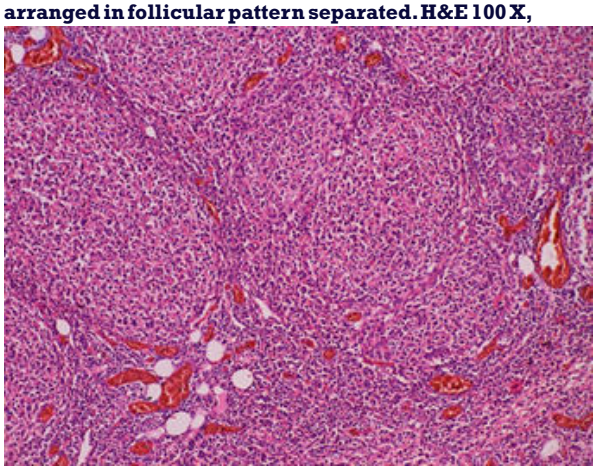
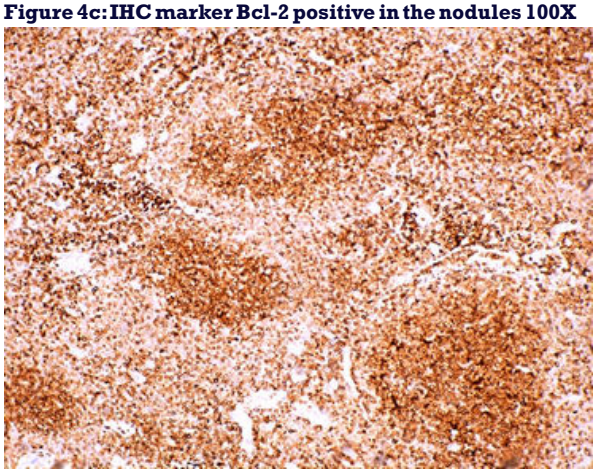


Figure 4c: IHC marker Bcl-2 positive in the nodules 100X



Mantle cell lymphoma[6,13]

We had one case of MCL in a 64 year old lady, who presented with abdominal discomfort. MCL is a mature B cell neoplasm composed of a monomorphic population of small to medium sized lymphoid cells with irregular nuclear contours . They commonly express CD 5 and cyclin D1. MCL accounts for 3-10% of all lymphoid neoplasms. It is more common in males than in females with a median age of 60years. MCL of the gastrointestinal tract shows mainly superficial ulcers , large tumor masses and diffuse thickening of the GI mucosa. Its presentation as multiple intestinal polyps is distinctive , but not specific. Histologically they show a mantle zone .Nodular and diffuse patterns are seen. MCL express B-cell markers CD20 , CD 5 and CD43. CD23 , BCL-6 & CD10 are usually negative. Cyclin D1 over expression is seen in >95% of the cases , including those that are CD5 negative(Figure 5a-e). The characteristic translocation t(11,14)(q13;q32) between IGH gene and CCND1 is seen in >95%of the cases.

Figure 5a: Small intestinal mucosa shows lymphoid cells in a nodular and diffuse pattern, H&E 100X

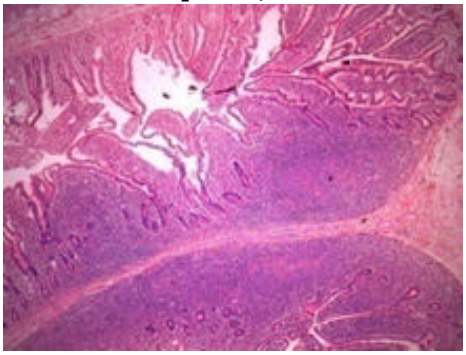


Figure 5b: IHC marker CD 5 positive in the lymphoid cells, 400X

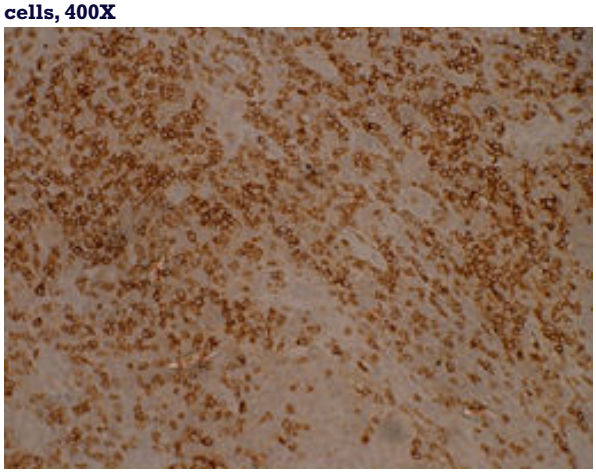
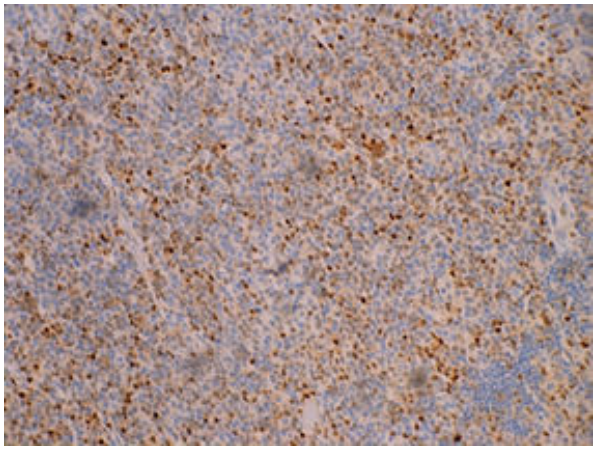


Figure 5c: IHC marker Cyclin D1 positive in the lymphoid cells, 200X



Extranodal Marginal Zone Lymphoma of Mucosa Associated Lymphoid Tissue[6,13]

Only one case of MALT lymphoma was diagnosed in this study. MALT is an extranodal low grade B cell lymphoma arising in mucosal or glandular tissue recapitulating the cyto-architectural features of MALT. Any part of the GI tract can be involved. Tumor can present as a superficial spreading mass forming lesion. Patient can be asymptomatic or show site specific symptoms. H.pylori association has been studied. In our case no H.pylori association was detected. MALT lymphoma is formed of small B cells. The cells typically include marginal zone cells, monocytoid cells and small lymphocytes. Plasma cell differentiation can be seen occasionally in MALT lymphoma of GIT. Lymphoid cells infiltrate around reactive lymphoid follicles in a marginal zone pattern , extending to the interfollicular region. Lymphoepithelial lesion i.e aggregates of >3 marginal zone cells with destruction of the glandular epithelium , along with eosinophilic degeneration of the epithelium can be seen. Lymphoepithelial lesions are less frequent in the non-gastric sites. Lymphoid cells are positive for CD20 , Bcl-2 and negative for BCL-6 ,CD5 and Cd10.

Intestinal T cell Lymphoma[13]

This study had one case of T cell lymphoma. The patients presented with loose stools and weight loss. Intestinal T cell Lymphoma is an aggressive GI lymphoma. Colon and small intestine are the most commonly affected areas. About 50% of the patients present with Stage III/IV diseases. Macroscopically, it can present with ulcerated plaque like appearance or as protruding luminal masses. Microscopically lymphoid cells can vary from small to medium to large lymphoid cells and show pleomorphism. Minority cases show epithelial infiltration (20%). Most common is CD4 positivity and CD4-/CD8-vity.

CONCLUSION :

GI lymphomas constitute a major type of extranodal lymphoma and 10-15% of Non-Hodgkin Lymphomas. High grade lymphomas are more common than low grade lymphomas. In this descriptive study , from a tertiary care centre, we have analyzed the clinical presentation , anatomical distribution, histological and immunophenotypical subtypes of GI lymphomas. In GI lymphomas for a precise diagnosis correlation of clinical findings with the morphology and immunophenotype is mandatory.

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