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Original Article

Pathology Section

Clinicopathological Study of Primary Gastrointestinal Lymphoma from a Tertiary Care Hospital in Southern India

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ABSTRACT

Introduction: Primary Gastrointestinal Lymphoma (PGIL) is a heterogeneous disease in terms of patient characteristics, site, histologic types and treatment modalities. Although rare disease, it is the most common site for extranodal lymphomas accounting for 10-15% of all Non-Hodgkin lymphoma and 30-40% of all extranodal lymphoma.

Aim: To study the different types of PGIL and its anatomic distribution along with its association with the clinical outcomes.

Materials and Methods: This was a retrospective study conducted in Department of Pathology of a tertiary care hospital, South India over a period of five years (2009 to 2013). A total of 61 cases of PGIL were identified, which included both resected surgical and endoscopic biopsy specimens. Histopathological classification of all cases was done based on morphologic and immunophenotypic criteria according to latest World Health Organisation (WHO) 2008 classification. Anatomic distribution of various types of lymphoma and associated clinical features were studied. The cases were then followed-up and survival analysis was also done. Descriptive statistical analysis methods were used to analyse the data. Overall Survival (OS) rates were calculated using Kaplan Meier method for 33 cases.

Results: There was predominance of men with peak incidence in 7th decade. Abdominal pain was the commonest presenting symptom seen in 77% of the cases. The most common site of involvement was stomach (41%) followed by large intestine (37.7%). All cases of primary GI lymphomas were of Non-Hodgkin type. B cell lymphomas (n=54; 88.5%) were more frequent than T cell lymphomas (n=7; 11.5%). Diffuse Large B Cell Lymphoma (DLBCL) was the most common subtype accounting for 67.2% of cases (n=41) followed by MALT lymphoma (n=9; 14.8%). Follow-up was possible in 33 cases out of which 20 patients (32.8%) died with a median overall survival period of 13 months (95% CI, 7.8-18.2). The five-year overall survival (OS) for 33 patients who were followed-up was 67.2%.

Conclusion: Diagnosing PGILs correctly according to the recent WHO classification is important so that correct treatment protocols can be followed.

Keywords: Burkitt lymphoma, Extranodal, Lymphoepithelial, Mantle cell, Non-Hodgkin

INTRODUCTION

Extranodal lymphoma is a well-known entity and is distinct from nodal lymphoma both in terms of treatment strategies and prognosis. It can involve any site but Gastrointestinal Tract (GIT) is the most common extranodal site involved by lymphoma accounting for 10-15% of all Non-Hodgkin lymphoma and 30-40% of all extranodal lymphoma. Although lymphoma can involve any part of the gastrointestinal tract, the most common site is stomach followed by small intestine [1].

The PGILs are those which predominantly involve the alimentary tract or those with symptoms of GIT involvement on presentation [2]. The criteria described by Dawson IM et al., can be used for distinction between primary and secondary GIT lymphomas, that include (1) absence of peripheral lymphadenopathy at the time of presentation; (2) lack of enlarged mediastinal lymph nodes; (3) normal total and differential white blood cell count; (4) predominance of bowel lesion at the time of laparotomy with only lymph nodes obviously affected in the immediate vicinity; and (5) no lymphomatous involvement of liver and spleen [3].

There is considerable variation in the literature with respect to the anatomic distribution and the various histopathological subtypes of PGIL worldwide [2,3].

Aim of this study was to ascertain the histological subtypes and sites of PGIL diagnosed at present institution and to associate it with the clinical features and outcome.

MATERIALS AND METHODS

It was a retrospective study of cases of GIT lymphoma diagnosed over a period of five-years in Department of Pathology, Kasturba Medical College, Manipal, Karnataka, India, from January 2009 to December 2013. The analysis of the data was done in April 2014. A total of 66 cases were identified out of which five were secondary GI lymphoma cases and rest 61 were PGIL. Ethical clearance was obtained from the Institutional Ethics Committee (IEC 333/2012).

Inclusion criteria: A total of 61 cases of PGIL were included in the study which comprised of both resected surgical and endoscopic biopsy specimens.

Exclusion criteria: Repeat biopsies or multiple biopsies from single patient were excluded from this study. Five cases of secondary GI lymphoma were also excluded based on Dawson's criteria [3].

Computerised database of all the patients, histopathology slides, Immunohistochemistry (IHC) slides and medical records were analysed. All 61 PGIL cases were reviewed and reclassified according to recent WHO 2008 classification [4]. Tissue sections were routinely processed and stained with Haematoxylin and Eosin (H&E). IHC was done judiciously depending on the H&E morphology and included CD3, CD20, CD79a, CD30, CD10, BCL 2, BCL 6, cyclin D1 and Ki-67. Due to financial constraints for IHC staining, it was not possible to classify and sub-classify some cases. Among the 61 cases of PGIL, follow-up was available only for 33 cases. The remaining patients of the total series were lost to follow-up during the five year interval.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) 12.0 software was used for the statistical analysis to determine the percentage frequency distribution of cases. OS was calculated using Kaplan Meier method for 33 cases.

RESULTS

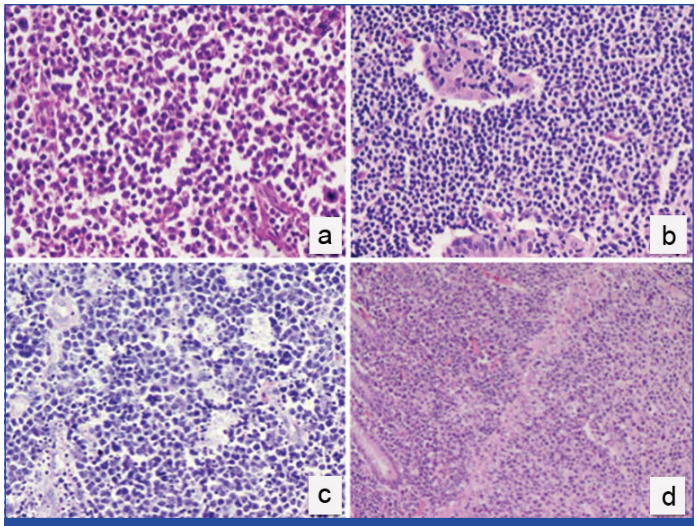
During five years, 61 PGILs were identified out of which 40 were men and 21 were women with men to women ratio of 1.9:1. Majority of PGIL were seen in elderly with a peak incidence in the seventh decade (median age - 46 years and range of 3-85 years) [Table/Fig-1].

Age range (years)	Number of cases	Percentage
0-10	4	6.5
11-20	0	0
21-30	7	11.5
31-40	10	16.4
41-50	14	23.0
51-60	5	8.2
61-70	17	27.9
71-80	3	4.9
81-90	1	1.6

[Table/Fig-1]: Age distribution of the study participants.

The most common presenting symptom was abdominal pain (n=47; 77%) followed by vomiting (n=13; 21.3%). Few cases presented with other symptoms such as diarrhoea (n=11; 18%), weight loss (n=12; 19.7%), fever (n=4; 6.6%) and abdominal mass (n=5; 8.2%).

The most common site for PGILs was stomach (n=25;41%) followed by large intestine (n=23; 37.7%) and included caecum (7), colon (11) and rectum (5) [Table/Fig-2]. Twelve cases (19.7%) of small intestinal lymphoma and included duodenum (4), jejunum (1) and ileum (7) were seen and only one case (1.6%) out of 61 cases primarily involved anal canal. No case of oesophageal lymphoma was found.

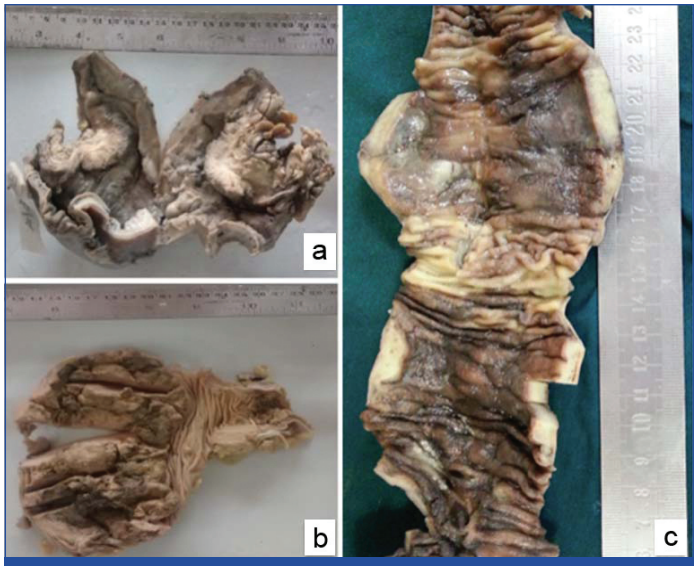


[Table/Fig-2]: a) Diffuse large B cell lymphoma (H&E, X200); b) MALT lymphoma-lymphoepithelial island (H&E, X200); c) Burkitt lymphoma-starry sky pattern (H&E, X200); d) Enteropathy associated T cell lymphoma-invasion of muscularis mucosae (H&E, X200).

All cases of PGIL in present study were of Non-Hodgkin type and predominantly were B cell lymphomas (n=54; 88.5%). T cell lymphomas were infrequent and constituted only 11.5% (n=7). DLBCL was the most common subtype accounting for 67.2% of cases (n=41). Second in frequency was low grade marginal zone lymphoma of Mucosa Associated Lymphoid Tissue (MALT) type (n=9; 14.8%) followed by T-cell lymphoma (n=7; 11.5%) [Table/Fig-3,4].

Most DLBCL (n=19) and extranodal marginal zone lymphoma of MALT type (n=4) were located in stomach. Five cases of MALT lymphoma had origin in large intestine which included colon and rectum. One case of follicular lymphoma involving the duodenum was seen.

Simultaneous *Helicobacter pylori (H. pylori)* infection was identified in seven (11.47%) cases of PGILs on histologic sections. Out of these four were DLBCL, two were MALT lymphoma and one was follicular lymphoma. Rest seven cases of MALT lymphoma were not associated with *H. pylori* infection.



[Table/Fig-3]: a) Nodular growth arising from stomach. On histopathological examination-Diffuse large B cell lymphoma; b) Ulcero-proliferative growth arising from transverse colon. On histopathological examination-Diffuse large B cell lymphoma; c) Diffuse thickening of the wall of intestine. On histopathological examination-Enteropathy associated T cell lymphoma.

Diagnosis	Frequency	Percentage
Diffuse large B cell lymphoma (DLBCL)	41	67.2
Low grade marginal zone lymphoma of MALT type	9	14.8
T-cell lymphoma	7	11.5
Burkitt lymphoma	1	1.6
DLBCL/Burkitt lymphoma	1	1.6
Mantle cell lymphoma	1	1.6
Follicular lymphoma	1	1.6

[Table/Fig-4]: Frequency of various histological subtypes of PGILs in the present study based on WHO 2008 classification.

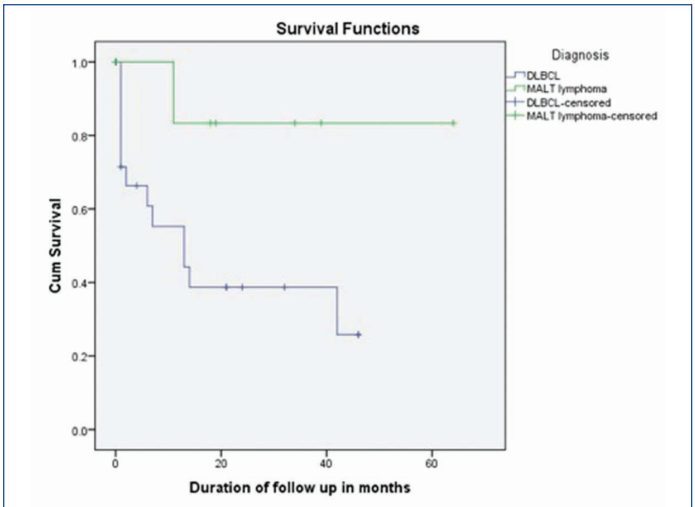
Human Immunodeficiency Virus (HIV) infection was associated with 11.47% (n=7) of the PGILs. Five cases (71.4%) were B cell type lymphoma and rest two (28.6%) were T cell type. All B cell lymphomas were of DLBCL type (n=5, 71.42%).

The patients were followed-up for a range of 1-64 months. At the last documented follow-up maximum cases (n=28; 45.9) were lost to follow-up as they did not return back for treatment, 20 patients (32.8%) died due to various causes [Table/Fig-5] with a median overall survival period of 13 months (95% CI, 7.8-18.2). The most common cause of death in patients with PGILs in the present study was respiratory failure (n=7; 35%) followed by septic shock (n=4; 20%).

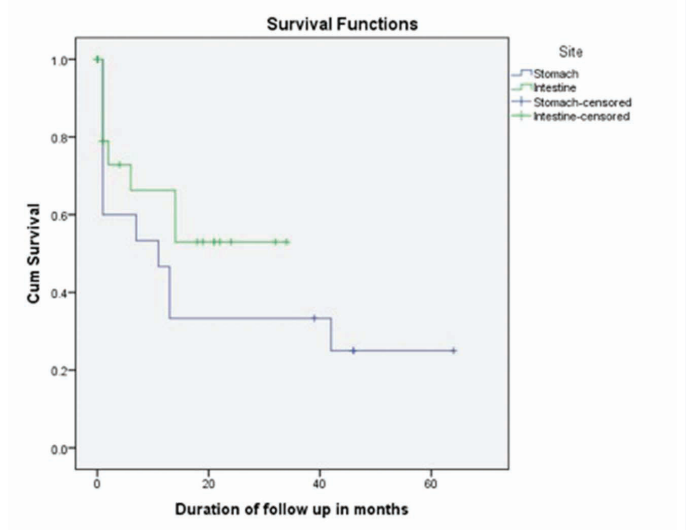
Cause of death	Frequency	Percentage
Cardiac arrest	3	15
Respiratory failure	7	35
GI bleed	2	10
Persistent diarrhoea	3	15
GI perforation	1	5
Septic shock	4	20

[Table/Fig-5]: Cause of death in patients with PGILs in this study.

The five-year OS for 33 patients who were followed-up was 67.2%. The OS in patients with MALT lymphoma (88.9%) was longer than patients with DLBCL (68.3%) (p=0.062) but a significant association could not be established [Table/Fig-6]. Similarly age, gender and site of origin of tumour also had no significant impact on overall survival in this study [Table/Fig-7,8].



[Table/Fig-6]: Kaplan Meier survival curve for comparison of overall survival between DLBCL and MALT lymphoma.



[Table/Fig-7]: Kaplan Meier survival curve for overall survival according to site of origin of the tumour.

Variable	No of patients (%)	Overall survival	
		5-year (%)	p-value
Sex			
Men	40 (65.5)	72.5	0.389
Women	21 (34.4)	57.1	
Age (years)			
≤60	40 (65.5)	67.5	0.744
>60	21 (34.4)	66.7	
Site*			
Stomach	25 (40.9)	56	0.224
Intestine	35 (57.4)	77	
Histological type@			
DLBCL	41 (67.2)	68.3	0.062
MALT	9 (14.8)	88.9	

[Table/Fig-8]: Univariate analysis of factors influencing overall survival of 33 patients with PGILs.
*One involved anal canal; @calculated overall survival only for the most common lymphomas

DISCUSSION

The PGIL is a heterogeneous disease in terms of patient characteristics, site, histologic types and treatment modalities. It accounts for 1-4% of all GI malignancies and is a rare disease [5]. However it is the most common site for extranodal lymphomas. Non-Hodgkin lymphomas are the predominant type of lymphomas occurring in GIT although few cases of Hodgkin lymphoma have been reported in literature [6].

The distribution of age and sex in the study was similar to that observed in various other Indian and Western studies. Abdominal pain occurred as the most common symptom in almost every study and this study also confirmed the same [Table/Fig-9] [7-11].

Author	Total number	Sex ratio (M: F)	Median age	Most common presenting symptom
Arora N et al., [7]	336	4.3: 1	45	-
Raina V et al., [8]	77	2.2: 1	32	Abdominal pain (81%)
Li M et al., [9]	216	2.9: 1	50	Abdominal pain (75.9%)
Morton JE et al., [10]	175	1.9: 1	-	Abdominal pain (45%)
Singh DP et al., [11]	75	1.9: 1	34	Abdominal pain (89%)
Present study	61	1.9: 1	46	Abdominal pain (77%)

[Table/Fig-9]: Comparison of age and sex distribution in the present study with other Indian and Western literature [7-11].

The most common site of involvement was stomach (41%) in this study similar to other Indian and Western studies [Table/Fig-10] [7,8,10-13]. The second in frequency was large intestinal lymphoma in contrast to studies conducted by Arora N et al., Raina V et al., Singh DP et al., and Koch P et al., where gastric lymphoma was followed by small intestinal lymphoma [7,8,11,12]. Saber MM et al., similar to this study reported higher incidence of large bowel lymphomas than small bowel lymphomas and the explanation given was exclusion of paediatric patients where intestinal lymphoma predominate [13]. In this study there were only four paediatric patients so the same explanation may hold true. However this may be a random variation due to limited number of cases. According to Koch P et al., ileocaecal and rectal lymphomas should be considered separately as they allow localised treatment and resection, especially in low grade lymphomas [12]. In this study ileocaecal and rectal lymphomas accounted for 22.9% and 8.2% respectively.

Author	Country	Stomach	Small intestine	Ileo-caecal	Large intestine
Arora N et al., [7]	India	53.6%	23.51%	10.12%	10.1%
Raina V et al., [8]	India	46.7	36.3%	-	17%
Morton JE et al., [10]	UK	45%	33.1%	-	26.8%
Singh DP et al., [11]	India	34.7%	22.6%	24%	18.6%
Koch P et al., [12]	Germany	74.7%	8.6%	7%	2.4%
Saber MM et al., [13]	Egypt	69%	4%	-	27%
Present study	India	41%	8.2%	22.9%	26.2%

[Table/Fig-10]: Comparison of site distribution of cases in present study with various studies [7,8,10-13].

Primary gastrointestinal T cell lymphomas are rare and occurred in 11.5% of patients, similar to other studies [Table/Fig-11] [7,14-19]. The most common histological subtype in this study and various other studies [7,13,15,18,19] was DLBCL followed by MALT lymphoma. Higher incidence of MALT lymphoma (44%) was reported by Nakamura S et al., [17]. They have attributed it to increase in *H. pylori* infection and advancement in diagnostic procedures. Rectal MALT comprised two out of nine cases (22.2%) in the present study. This was in concordance with study by Kohno S et al., (23%) [16]. In a study by Geramizadeh B and Keshtkar Jahromi M conducted in Iran, small intestinal MALT lymphomas were more common than gastric MALT lymphomas [15]. This is due to the prevalence of IPSID (Immunoproliferative Small Intestinal Disease) in Middle Eastern countries. There was not a single case of IPSID in this study which can be attributed to geographic variation or can be due to small sample size. Burkitt lymphoma accounted for only 3.2% in the study in contrast to studies by Arora N et al., (10%), Shukla K et al., (36%) and Kohno S et al., (11.2%) [7,14,16]. This may be again due to less number of paediatric cases. 85.7% (n=6 out of 7 cases) of T cell lymphomas occurred in individuals more

than 40 years and small intestine was the most frequent location. The term "Enteropathy Associated T cell Lymphoma" (EATL) was introduced by O'Farrelly C et al., in 1986 and its association with celiac disease was pointed out [20]. In the present series one case of primary intestinal T cell lymphoma associated with tropical sprue was identified, however complete immunohistochemical work up was not done to further subtype it due to financial constraints. In this case, mucosa adjacent to primary tumour showed villous atrophy, crypt hyperplasia and intraepithelial lymphocytosis. Apart from this, there was a single case of EATL type -1 in a 62 years old woman who presented with complaints of fever and loose stools. No histological evidence of celiac disease was noted but the tumour cells were CD3 positive and negative for CD4, CD 8, CD 56 and TCR-β.

Author	DLBCL	MALT lymphoma	Burkitt lymphoma and DLBCL/BL	T-cell lymphoma
Aroma N et al., [7]	66.7%	10.1%	10.5%	3.3%
Shukla K et al., [14]	36%	16%	36%	4%
Geramizadeh B et al., [15]	65.5%	20%	10%	1.8%
Kohno S et al., [16]	58.7%	7%	11.2%	14.7%
Nakamura S et al., [17]	38.5%	44%	1.3%	9%
Kumar RN [18]	72.2%	25%	-	-
Al-Sayes FM [19]	60.9%	39.1%	-	-
Present study	67.2%	14.8%	3.2%	11.5%

[Table/Fig-11]: Comparison of histological subtypes of PGILs [7,14-19].

Non-Hodgkin lymphomas represent a common malignancy in Acquired Immunodeficiency Syndrome (AIDS) patients. DLBCL is the most common primary GI lymphoma seen in association with AIDS [21]. The other histological subtype seen in AIDS patients in this study was T cell lymphoma (n=2; 28.6%). The absence of lymphoblastic lymphomas, post-transplant lymphoproliferative disorder and plasmablastic lymphomas in this study can be attributed to rarity of these diseases and the smaller sample size.

Associated *H. pylori* infection was identified using Warthin-Starry stain on tissue section and was seen in only 11.5% (n=7) of cases. Out of these, four were DLBCL (57.1%), two were MALT lymphomas (28.57) and one was follicular lymphoma (14.3%). This was much less compared to various other studies. The low incidence of *H. pylori* in this study could be due to availability of only histopathological examination as serology was not available. Serology tests are mandatory when histology is negative as they increase the sensitivity [7]. Detection of *H. pylori* is important as recommended strategy for management of early stage *H. pylori* positive gastric MALT lymphoma is eradication of bacilli with antibiotics [18].

The five-year overall survival in this study was 67.2%. It was higher than those documented in other studies [Table/Fig-12] [9,13,22-24]. This can be due to various risk factors in different series of cases which is not taken into account while computing OS. Univariate analysis of factors considered as predictors of OS was done in this series of cases but none of them had significant impact on OS [Table/Fig-8]. The OS in patients with MALT lymphoma (88.9%) was longer than patients with DLBCL (68.3%) (p=0.062) but a significant association could not be established. Conversely in this study the OS of patients with age group ≤60 years (67.5) was almost equal to those with age group >60 years (66.7). This can be attributed to more number of patients in age group ≤60 years (n=40) than age group >60 years. In future, a multicentric study with larger sample size is required to analyse statistical significance of the parameters affecting the overall survival of the patients.

Authors	Country	Overall survival (5-year)
Li M et al., [9]	South China	56.4
Saber MM et al., [13]	Egypt	45%
Chandran RR et al., [22]	India	47%
Atalay C et al., [23]	Turkey	58.5%
Huang JJ et al., [24]	China	59%
Present study	India	67.2%

[Table/Fig-12]: Comparison of overall survival in patients with PGILs [9,13,22-24].

Limitation(s)

Limitation of this study was small sample size as the data was obtained from a single tertiary care centre. Many patients were lost to follow-up as they did not return back for treatment, so significant association between OS and other factors, considered as predictors of OS could not be established.

CONCLUSION(S)

The PGIL are rare and diagnosing them correctly according to the recent WHO classification is important so that correct treatment protocols can be followed. There is a close connection between chronic inflammation and lymphomas in gastrointestinal tract, so better understanding of its aetiology and molecular aspect is required. Information of the HIV status of the patient or any other type of immunodeficiency (post-transplant) should be available to avoid misdiagnosis of unusual lymphomas which have poorer prognosis than usual types.

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