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A HISTOMORPHOLOGICAL STUDY OF GASTRO-INTESTINAL LYMPHOMAS - AN ANALYSIS OF 47 CASES

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Abstract :
BACKGROUND AND OBJECTIVES - The Gastro-intestinal tract forms the commonest site of extra nodal lymphoma and is the second most common extra nodal lymphoma in AIDS patients. This study analyses the clinical and pathological findings of 47 patients diagnosed with gastrointestinal lymphomas, in our hospital, a tertiary care centre in South India. MATERIALS AND METHODS - The clinical and histopathological materials of 47 patients diagnosed with gastrointestinal lymphomas from January 2008 to July 2012 were considered for study. The pathologic findings including immunohistochemical profile were analyzed. RESULTS - Of 47 cases, all were primary lymphomas with 57.45 percent occurring in males and 42.55 percent in females. Male female ratio is 1.35 is to 1. The mean age was 40.15 yrs. The most common site of involvement was stomach (18 cases) followed by small intestine (12 cases) and large intestine (10 cases).The commonest gross presentation was nodular lesion. Using Working classification for clinical usage, the grading of lymphomas was done and included 7 low grade, 31 intermediate grade and 9 high grade lymphomas. B cell lymphomas constituted 94.3 percent cases (33 cases) while T cell lymphomas constituted 5.7 percent cases (2 cases), after exclusion of 12 cases in which IHC markers were not done. Histologically, all were diffuse lymphomas with features of MALT lymphomas seen in 5 cases, Diffuse Large B Cell Lymphomas (DLBCL) in 9 cases and Immunoproliferative small intestinal disease (IPSID) in 3 cases. As a comprehensive Immunohistochemical panel was not available, further typing of lymphomas including rarer types was not possible.CONCLUSION - The study highlights the increasing incidence of lymphomas with various types of gross presentation. The results parallel those of Western literature with B cell lymphomas especially DLBCL being the commonest. Cases of Immunoproliferative small intestinal disease which are reported in certain geographically restricted locations are also seen in our study. A definitive diagnosis rests on combined histologic, immunohistochemical and molecular studies.
Keyword : Gastro-Intestinal Lymphoma, Histomorphology, Diffuse Large B Cell Lymphoma

INTRODUCTION:

Gastrointestinal lymphomas constitute a spectrum of diseases with majority being formed by Diffuse Large B Cell Lymphomas and MALT lymphomas. GI lymphomas form 10 – 15% of all Non-Hodgkin's Lymphomas and 30 – 40% of all extra nodal lymphomas[1, 2]. The incidence of GI lymphomas has been on the rising trend, with considerable differences in site of occurrence and type of lymphomas in various geographical locations[3]. They also form the second commonest extra nodal lymphoma in AIDS patients in whom anorectal involvement is more common. Various classifications have been proposed with the recent one being WHO classification which is based on morphological, immunophenotypic, genetic and clinical features. Primary gastrointestinal lymphomas have been defined by Dawson et al[4] as tumor with the following features: Predominant involvement of gastrointestinal tract, involvement of lymph nodes draining the primary tumor site; no hepatic or splenic involvement or palpable lymphadenopathy; Normal chest X ray and peripheral WBC count. This study reviews the clinicopathological data of 47 patients diagnosed with GI lymphomas over a period of 4½ yrs. in our hospital, a tertiary care center in South India. The data has been analyzed by age, sex, gross and microscopic features, immunohistochemical findings and associated co-morbidities.

MATERIALS & METHODS:

A study of 47 patients with GI lymphomas covering the period from January 2008 to July 2012 was done in our hospital. Clinical details including the age, sex, symptoms and radiological findings were evaluated. The gross findings and histological types were reviewed along with immunohistochemical data. The histology was studied using Hematoxylin and Eosin stained 5 micron sections of paraffin blocks in which tissues fixed in 10% Neutral Buffered Formalin and processed were embedded. The histological grading was done using Working Formulation for clinical usage, as comprehensive immunohistochemical panel for diagnosis as per WHO classification were not available. Immunohistochemical markers used were CD3, CD20, CD45 and CK/EMA.

OBSERVATIONS:
INCIDENCE AND CLINICAL PRESENTATION:

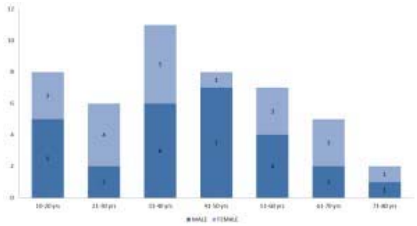


Fig. 1 Age and sex distribution

Out of 44236 surgical specimens received, 47 cases were GI lymphomas, thus constituting 0.11%. The mean age of presentation was 40.15 yrs; Males outnumbered females (27 vs 20 cases) in the ratio 1.35:1(Fig. 1). Clinical presentations included abdominal pain, bleeding per rectum, melena, weight loss and recurrent jaundice. Three patients diagnosed with IPSID presented with watery diarrhea, abdominal pain and loss of weight. Two patients were HIV positive and were on anti-retroviral treatment at the time of presentation.

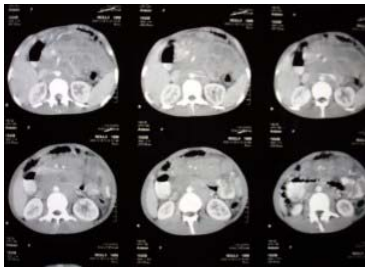


FIG. 2 CT scan abdomen – Duodenal lymphoma

2. GROSS FEATURES:

The various gross presentations are listed in Table 1 in the descending order of frequency. As noted,
the commonest presentation was nodules (Fig. 4). The largest dimensions recorded were 12 cm x 10 cm. The predominant site of involvement was stomach (18 cases). The distribution of lesions is shown in Table 2.
Table 1. GROSS APPEARANCE

GROSS APPEARANCE	FREQUENCY
Nodules	17
Ulceroproliferative	11
Proliferative	7
Ulcers	6 (one showed perforation – Fig.3)
Circumferential	3 (one as stricture)
Erythematous nodule	2
Polypoid	1

Circumferential	3 (one as stricture)
Erythematous nodule	2
Polypoid	1

DISTRIBUTION	FREQUENCY
Stomach	18
Small intestine	12
Large intestine	10
Small & large intestine (ileocaecal region)	6
Multifocal	1

FIG. 3 Jejunal lymphoma presenting as ulcer with perforation(arrow)

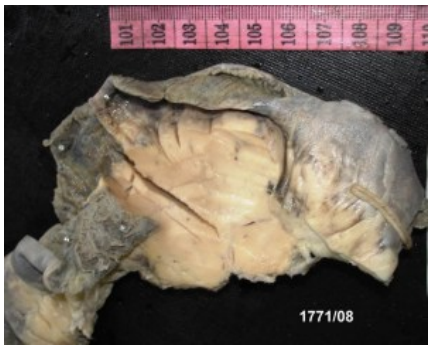


FIG. 4 Small bowel lymphoma presenting as nodular lesion

3. MICROSCOPIC FEATURES:

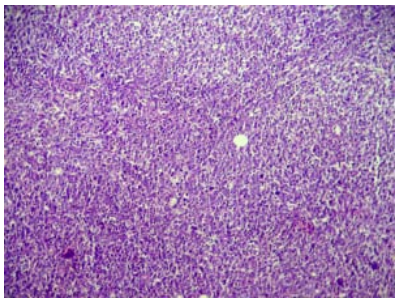
All were diffuse lymphomas with none showing follicular pattern. The histologic types and their distribution are shown in Table 3. Diffuse Large B Cell Lymphoma (DLBCL Fig. 5 to 8) and MALT lymphomas (Fig.9 & 10) were seen in stomach, DLBCL and IPSID (Fig. 11) in the small intestine; 2 cases of Maltoma in the large intestine and 2 cases of DLBCL in the ileocaecal region were reported. A multicentric tumor involving stomach and large intestine showed features of DLBCL. Table 3. HISTOLOGIC TYPES

	STOMACH	SMALL INTESTINE	LARGE INTES-TINE	SMALL & LARGE INTESTINE	MULTIFOCAL
DLBCL	5	1	-	2	1
MALTOMA	3	-	2	-	-
IPSID	-	3	-	-	-
NO SPECIFIC FEATURES	10	8	8	4	-
TOTAL	18	12	10	6	1

The grading of the lymphomas is shown in Table 4. Majority were Intermediate grade (31 cases - 65.95%).
Table 4. GRADING

GRADE	STOMACH	SI	LI	SI+LI	MUTIFOCAL	TOTAL
LOW	2	2	3	-	-	7
INTERMEDIA TE	11	9	7	4	-	31
HIGH	5	1	-	2	1	9
TOTAL	18	12	10	6	1	47

SI – small intestine; LI – large intestine



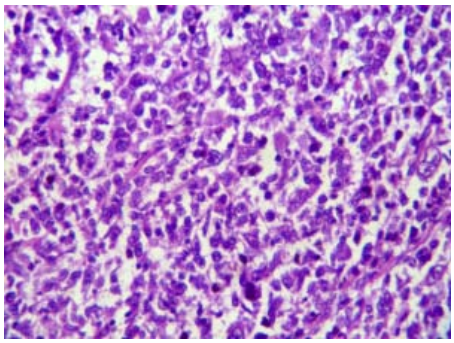
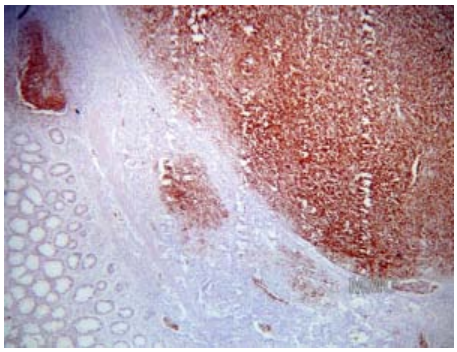
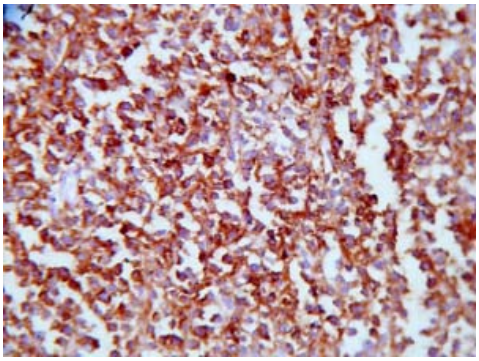
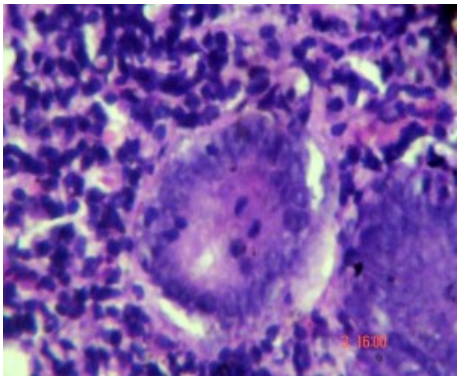
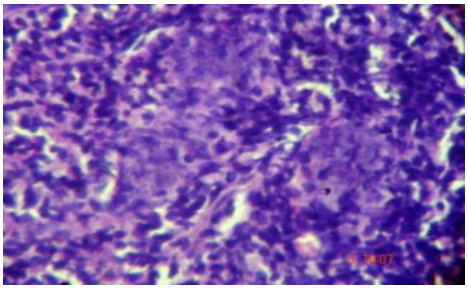


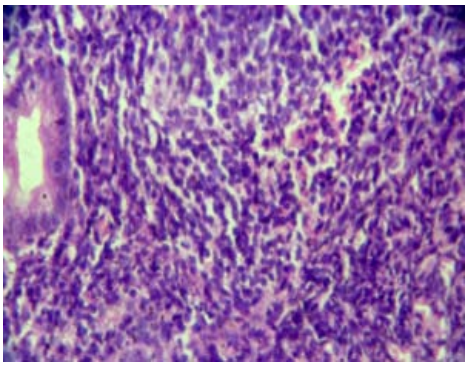
FIG. 5 DLBCL large bowel. H & E x100
FIG. 6 DLBCL large bowel. H & E x400
FIG. 7 : CD 20 (same case as fig.5 & 6) – strong diffuse positivity x 100
FIG. 8 : CD 20 – strong diffuse positivity x 400
FIG. 9 MALTOMA stomach-showing intra-epithelial lympho-cytes H & E x400





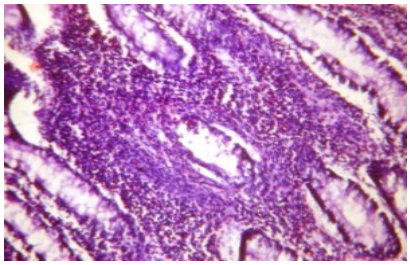






4. IMMUNOHISTOCHEMISTRY:

Immunohistochemistry done to determine lineage in 35 cases showed 94.3% (33 cases) of B cell lymphomas and 5.7% (2 cases) of T cell lymphomas (Fig 12 to 14).



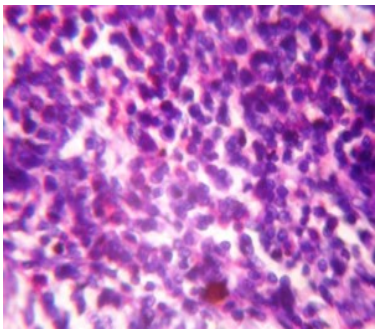
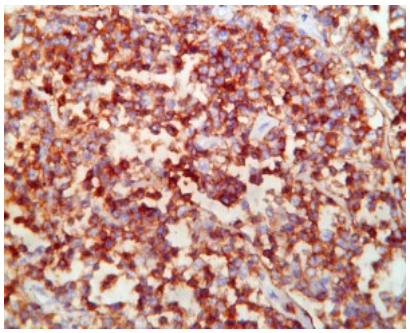


FIG. 13 T cell lymphoma ileum H & E x400



5. CO-MORBIDITIES:

Two patients in our study were HIV positive and were receiving Anti-retroviral treatment. The first patient was 10 yr. female child who presented with abdominal mass; no hepatosplenomegaly or significant lymphadenopathy was present. Her CD4 count was 426 cells/mm^3. A CT guided biopsy was done and showed features of Non-Hodgkin's Lymphoma Intermediate grade. Immunohistochemistry was not possible due to inadequate material. The second patient was a 35 yr. female patient with abdominal pain. Her CD4 count was 508 cells/mm^3. Colonoscopy revealed a proliferative growth in ileocaecal region measuring 13cmx12cm along with multiple nodules in the colon. HPE and IHC showed features of DLBCL.

DISCUSSION

Gastrointestinal lymphomas constitute 1 to 4% of all GI malignancies[5]. Worldwide, the incidence of lymphomas has been increasing with new cases of extranodal lymphomas reported at a rate of 3 to 6.9% annually[6]. GI lymphomas are usually seen in middle aged and elderly, though they may occur at any age. Special types such as IPSID and Burkitt's lymphomas are seen in children and young adults. A male predominance is seen in most GI lymphomas. The commonest site of involvement in many studies is the stomach, followed by small intestine, ileocaecal region and colon[7, 8]. GI lymphomas commonly present with abdominal pain[9]. Other symptoms include dysphagia, abdominal mass, GI bleeding, weight loss, intestinal obstruction or perforation depending on the type and site of lymphomas[10]. Specific symptoms like malabsorption and right iliac fossa mass (ileocaecal involvement) are seen in IPSID and Burkitt' lymphoma respectively. The different non-invasive staging procedures that can be used include Endoscopic Ultrasonography (EUS), CT (Fig.2), MRI, FDG-PET, and molecular markers[11, 12]. Newer promising techniques on the horizon include hybrid PET-CT imaging and PET tracers like 18F-Fluorothymidine[13]. The variable ulceroproliferative, polypoidal, excavating or nodular morphology of GI lymphomas may mimic any other neoplastic lesion of gastrointestinal tract (Fig.3 & 4). In our study, nodular lesions were the commonest. B cell lymphomas are much more common than T cell lymphomas, with DLBCL being the commonest[14]. The other rarer types include Burkitt's lymphoma, Follicular lymphoma, Mantle cell lymphomas, T cell lymphomas and Hodgkin's lymphoma. Diffuse large cell B cell lymphomas (Fig.5 & 6) are characterized microscopically by diffuse sheets of large cells with narrow distinct rim of cytoplasm, round, oval, irregular, or lobated nuclei and 1-3 distinct nucleoli. They may show transmural involvement with or without perforation. Anorectal DLBCL may show plasmablastic morphology. MALT lymphomas are commonest in stomach and are usually confined to gastric mucosa or submucosa. Microscopic examination (Fig.9 & 10) shows a polymorphous population composed of small lymphocytes, marginal zone B cells and plasma cells. Reactive follicles and lymphoepithelial lesions are characteristic, the latter showing clusters of neoplastic cells infiltrating and destroying the glands. IPSID affects males and females equally and shows blunting of villi with dense, continuous, band like mucosal lymphoid or lymphoplasmacytic infiltrate (Fig.11) that is uninterrupted along the length of the small intestine. It is also called as alpha chain disease. Burkitt's lymphoma is a highly aggressive, rapidly growing tumor. Histologically, medium-sized atypical lymphoid cells with basophilic cytoplasm, round nuclei and and 3 to 4 small nucleoli are seen. Numerous tingible body macrophages giving a starry-sky pattern are also seen. Three clinical variants are described: endemic, sporadic and immunodeficiency associated. Intestinal T cell lymphoma, usually occur as a complication of Gluten sensitive enteropathy. The incidence is 5% and the commonest site of involvement is proximal jejunum. 40% present as abdominal emergency, because of adhesions. Lymphoma cells invade epithelium along with inflammatory cells, especially with eosinophils (Fig.12 & 13). The incidence of gastrointestinal involvement in HIV patients has been reported up to 30%[15]. HIV infected patients are at 50 to 60 times higher risk of acquiring lymphomas than the general population. The commonest sites of involvement are colon and anorectal area, followed by the small intestine and rarely stomach. Most are high-grade B cell lymphomas especially Diffuse large B-cell lymphoma of immunoblastic type and are more often EBV+ than lymphoma in the general population. In conclusion, GI lymphomas show increasing incidence and heterogeneous presentation. The results parallel those of Western literature with B cell lymphomas, especially DLBCL being the commonest. Immunoproliferative small intestinal disease which has been reported initially in the Mediterranean regions has also been encountered in our study. In the era of targeted therapy, an accurate diagnosis is needed and requires a combination of histological, immunohistochemical and molecular studies.

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