Clinicopathologic characteristics and therapeutic outcome of primary gastrointestinal lymphoma in cuddalore district in India.

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ABSTRACT

Objectives: The aim of the study is to determine the clinico-pathological features and therapeutic outcome of primary gastrointestinal lymphoma (PGIL) at a tertiary care hospital at Cuddalore district, India. Materials and methods: 36 patients with primary Gastrointestinal lymphoma (PGIL) diagnosed over a 6 year period from 2003 to 2008 were retrospectively and prospectively studied clinically and histopathologically and a followup was done for minimum of three years till 2010 they were classified using the REAL/WHO histopathologic classification and follow up was done for a minimum period of 3 years. Results: 36 patient (38.7%) were PGIL arising out of 93 total lymphomas diagnosed. Out of 980 primary gastrointestinal malignancies, 36(3.6%) were PGIL, with a male to female ratio of 1.5:1. All the patient were non vegetarians and majority of males were alcoholics and smokers. The mean age of the male patients was 61.3 years with age varying from 42 – 83 years with an SD of ±13.09: while for females, the mean age was 64 years, ranging from 50-75 years with an SD of ±9.14. Abdomen pain was the most common presenting symptom (70%), and the most common primary site was stomach (72.2%), followed by small bowel (16%), the important histological type was Non Hodgkins lymphoma (100%), no Hodgkins lymphoma was diagnosed. The predominant subtype was diffuse large B cell lymphoma accounting for 72.5% of the cases, followed by the marginal marginal zone cell lymphoma (25%) which was helicobacter associated (55%). A large proportion of patient with primary GIL had early disease (stage I E – 20 % and stage IIE 60%) . 17 (47.2%) Patient had chemotherapy, 11(30.5%) patients underwent gastrectomy followed by chemotherapy and only one patient was treated by HPeI eradication. The overall 3 survival rate was 58%. Conclusion: primary gastrointestinal lymphomas constitute about 3.6% of all gastric malignancies and Hodgkins lymphoma was nil and Non Hodgkins lymphoma constituted all the PGIL. Abdomen pain was the common presenting symptom and stomach being the commonly involved site and majority of cases presenting as exophytic mass. Diffuse large B cell lymphoma is the most common histological subtype, followed by extra nodal marginal zone B cell lymphoma(MALT) The majority of the cases have early disease( stage 1 and IIE), mostly treated by combination chemotherapy.

1. Introduction

GI Tract is the most common extranodal site involved by lymphoma accounting for 5 – 20% of all cases [1, 2, 3]. PGIL lymphoma are rare constituting only about 1% - 4% of all GI malignancies. The stomach is the most common location of GI lymphomas, followed by the small intestine 20 -30% [4,5,6,7] the colon and the rectum 10 –20%. 90 percent of the PGIL are of B cell lineage with very few T-cell lymphomas and Hodgkin lymphoma. Certain histological subtypes have been noted to have a relative predilection site as MALT lymphoma in stomach, mantle cell lymphoma in terminal ileum, jejenum and colon, as well as enteropathy- associated T cell lymphoma in jejenum, and follicular lymphoma in duodenum [8].

The esophagus is a rarely involved site, accounting for < 1% of all gastrointestinal lymphomas. Primary esophageal lymphoma is
extremely rare, with less than 30 cases reported in the literature\textsuperscript{[9,10,11]}. Primary gastric lymphomas (PGL) is the most common extranodal lymphoma, representing 30-40% of all extranodal lymphoma and about 60 – 75% of all gastro intestinal lymphomas \textsuperscript{[12,13,14]}. PGL constitute less than 15 percent of gastric malignancies and about 2 percent of all lymphomas \textsuperscript{[16]}. In PGL >90% cases are diffuse large B cell lymphoma (DLBCL) and marginal zone B-cell lymphoma of the Mucosa-associated lymphoid tissue tumor. \textsuperscript{[17,18]} Small intestinal lymphomas constitute 20 to 30 percent of all PGL \textsuperscript{[19,20]} and 11.8 percent of small intestinal tumors \textsuperscript{[19]}. The lymphomas of colorectal represents 0.2 – 0.4 % of all colorectal tumors \textsuperscript{[25,22]} and 20 to 30 percent of all colorectal lymphomas. Cecum followed by rectum are more frequently involved sites and predominantly of diffuse large cell lymphoma 40 percent and Burkitts lymphoma 60 percent \textsuperscript{[41]}

2. Material and Methods

A total of 36 patients with PGL diagnosed at a tertiary care hospital at cuddalore district, India over a period of 6 years were studied prospectively and retrospectively (2003 through 2008) and a followup was done for minimum three years till 2010. Medical records of all the patients were reviewed and clinical and pathological information was recored in a structured questionnaire form. The laboratory and radiological work-up included complete blood count, creatinine, liver enzymes, lactate dehydrogenase, uric acid, chest x ray, computed tomography of chest and abdomen, bone marrow biopsy and endoscopic evaluation with multiple biopsied of upper and lower GI tract.

2.1.Histology and immunohistochemistry

Tissue sections were obtained from formalin fixed paraffin blocks and stained with Hematoxylin and eosin. Special stains such as Periodic Acid – Schiff and reticulin stains were used in selected cases whenever indicated. Each biopsy was investigated immunohistochemically by staining for leukocyte common antigen, CD 20, CD 43, CD 138, and CD 45. Additionally Helicobacter pylori were demonstrated using either fast cresyl violet or giemsa stain.

3. Results

From the year 2003 through 2008, 36 patients with primary GI lymphoma were accrued to the study. Out of 980 gastrointestinal malignancies 36 were found to be lymphomas comprising about 3.6% of all GI malignancies. Twenty one patients were males and fifteen were females. The male to female ratio was 1.4:1. The mean age for male was 61.3 years ranging from 42 to 83, With a SD of ± 13.09 and for females the mean age was 64 years, ranging from 50 to 75 years with an SD of ± 9.14.

Abdominal pain was the most common presenting symptom(70%), followed by abdominal mass(20%).

Almost all the patient were non vegetarians and majority of them are mutton eaters. In male patients majority are alcoholic and smoker were as females were non alcoholics and non smokers. The most common site was stomach 72.2%, followed by the small bowel 16%. The third largest group of lymphoma originating in the colon 13.8%.

Symptoms such as fever, night sweats, weight loss occurred in 42% of cases. The mean time from onset of symptoms to diagnosis was 100 days.

Lactate dehydrogenase level was elevated in approximately 45% of patients, other laboratory tests including white blood cell, platelet count, uric acid level, creatinine and liver enzymes, were normal.

The most frequent histologic subtype was the diffuse large B cell lymphoma, accounting for 72.2% of all the cases; followed by MALT type lymphoma (25%) which corresponds to the marginal zone cell lymphoma in the REAL/WHO classification.

Most of the marginal zone lymphoma cell lymphomas (MALT type) were of gastric origin. Helicobacter pylori could be identified on histological sections in all the four cases; the serological test for H. Pylori was available only for three cases, which was positive. Gl endoscopy revealed exophytic mass in 50% of cases, and ulcerative lesion in 25% of cases and the rest as flat lesions.

According to the modified staging classification, a larger proportion of patients with GI lymphoma had early disease (stage I E - 20%, stage I E - 60%), while stages II E and IVE accounted for 4 and 18% respectively.

With regards to treatment, eleven patient (30.5%) had gastrectomy followed by chemotherapy, and six (16.6%) received multimodality treatment in the form of gastrectomy and chemotherapy followed by radiotherapy, seventeen patients (47.2%) of patients had chemotherapy only, and the remaining patients were treated with Helicoprylori pylori eradication. The mean follow up of was three years. The overall 3 year survival was 58%.

The outcome in patients with primary GI Lymphoma in relation to histology is shown in table.

Outcome of primary GI Lymphoma in relation to different histological subtypes.

<table>
<thead>
<tr>
<th>Marginal zone lymphoma</th>
<th>Diffuse large B cell lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients(n)</td>
<td>%</td>
</tr>
<tr>
<td>Cured</td>
<td>9</td>
</tr>
<tr>
<td>Remission</td>
<td>2</td>
</tr>
<tr>
<td>Relapse</td>
<td>2</td>
</tr>
<tr>
<td>Died</td>
<td>-</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>2</td>
</tr>
</tbody>
</table>

4. Discussion

Gastrointestinal lymphomas constitutes 1% to 4% of all gastrointestinal malignancies and it is common extranodal site of lymphoma and hodgkins lymphoma is rare in gastrointestinal lymphoma as comprising and non Hodgkins lymphoma constitutes the majority of all GI lymphomas. PGL is the most common extranodal lymphoma, representing 30-40% of all extranodal lymphoma and about 60 – 75% of all gastric malignancies \textsuperscript{[12,13,14,15]}
Males were affected more than females in our study 1.5:1 which is lower than what has been reported from Jordan [24] and the West [42] but it is close to the ratio reported from Thilland [26] and China [27].

The peak age of our patients was in the sixth decade, which is older than the age group of a previous study from the Kingdom of Saudi Arabia [28]. PGIL is rarely suspected because of the nonspecific presenting symptoms and signs [29]. Abdominal pain is the predominant occurring up to 93% of patients [30] in our study abdominal pain was the most common symptom at presentation followed by abdominal mass in 70% and 20% respectively. These results were similar to the previous results from KSA [28], Bahrain 21, United Arab Emirates, Jordan, Thailand, China, Japan and West.

Primary GI lymphoma is a heterogenous disease with regards to patient characteristics, stage, histological subtypes and treatment results [31].

The duration of symptoms is often long [30] in our series, median time from onset of symptoms to diagnosis is 100 days. This delay in presentation is because the diagnosis is rarely suspected due to the nonspecific symptoms of GI lymphoma.

Diffuse large cell B cell lymphoma is the commonest histological subtype of GI lymphoma in most of the series [24, 26, 27, 28, 30, 32]. It involves the MALT sites. In the current study diffuse large B cell lymphoma is the most common followed by extranodal marginal - zone B cell lymphoma which accompanies chronic gastritis in the presence of Helicobacter pylori infection. It accounts for about 40% of GI NHL [32]. In our current study accounts for about 42% and all of them were Helicobacter pylori positive on histological sections.

Our cases showed mass or filling defects in 80% of cases, followed by ulcerated lesion [15%] and diffuse thickening of the mucosa [5%]. Unlike a previous study from Saudi Arabia, were superficial and multicentric ulceration of mucosa was the most frequent endoscopic feature [33].

At presentation 79%, our patients had stage IE and II E. Two authors reported 87% [30, 34] and 89% which is comparable to our data.

Combined modality of approach that includes surgical debulking and systemic chemotherapy is the preferred treatment [35]. Different therapeutic approaches were used in two subsets: radical tumor resection (hemicolectomy) plus multiagent chemotherapy in advanced age patients [4, 5, 36]. Polychemotherapy includes CHOP (cyclophosphamide, doxorubicin, vincristin, and prednisolone) or CHOP like combination chemotherapy or MACOP-B like regimens [4, 5]. Surgery can be considered as an adequate treatment for patients with low - grade NHL disease that has not infiltrated beyond mucosa [25]. However, it is still thought that the prognosis of intestinal lymphomas is to surgery, therefore, it seems appropriate and cautious to resect intestinal lymphoma whenever possible. [37, 38]. Those with limited stage disease may enjoy prolonged survival when treated with aggressive chemotheraphy. [4]. Radiotherapy is beneficial for incomplete resection or nonresectable disease. Ileocecal region and cecum were the most frequent sites of involvement [76%], most patients had bulky disease. Diffuse large cell lymphoma was seen in 11 patients and peripheral T cell lymphoma in one patient. Three patients had mantle cell lymphoma and two had indolent lymphomas. [MALT -1 and small lymphocytic -1]. Eleven patients underwent hemicolectomy. Right side in nine left side in two, five diffuse large B cell lymphoma patients required emergency surgery for intestinal perforation. Due to the rarity of oesophageal lymphoma, no standard approaches to its management have been formulated, external beam radiation at the dose of 40 Gy can be used [39]. The patient was treated with initial radiotherapy followed by surgery an chemotheraphy in few cases and surgery along with chemotheraphy in some patients. Radiotherapy along with surgery and chemotheraphy prove better results than only with surgery and chemotheraphy.

The most widely recommended strategy for the management of early stage H. Pylori positive MALT type of gastric lymphoma is to eradicate H. Pylori with antibiotics and proton pump inhibitors. Although surgery has been used as its initial treatment, recent studies showed that radiotherapy alone can achieve a complete remission with a 5 year disease free period [40-43]. In present study majority of patients with gastric lymphoma were treated with chemomunotherapy with 4 cycles of R-CHOP (Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) followed by radiotheraphy. A complete remission was obtained and it was better than chemotherapy alone.

5. Conclusion

The current study showed that PGIL is commoner among males than females, the peak age being in the sixth decade. Abdominal pain is the common presenting symptom. The median time to the onset of symptoms to diagnosis is 100 days. The majority of patient were non alcoholic and non smokers. The disease showed non specific symptoms which lead to a delay in the time of diagnosis. Hodgkins lymphoma was nil in our study and the majority of lymphoma was gastric origin. Diffuse large B cell lymphoma represents the most common histological type, followed by extranodal marginal- zone B cell lymphoma and Helicobacter pylori associated lymphoma. Most of the lymphomas were detected at an early stage of the disease. The data presented here is an approximate assessment of the epidemiological features of primary GI which are needed to undertake definite preventive and therapeutic measures.
References


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