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Primary Intestinal Lymphomas – A Report of Four Cases

Medical Science

KEYWORDS : Intestine, MALToma, follfollicular lymphoma, mantle cell lymphoma

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ABSTRACT

Primary intestinal lymphoma is defined as an extranodal lymphoma arising in the intestine. World Health Organization (WHO) classifies intestinal B- cell lymphomas into MALT lymphoma, Immunoproliferative small intestinal disease (IPSID), Mantle cell lymphoma, Burkitt lymphoma and diffuse large B cell lymphoma. This study includes four primary intestinal lymphomas. All were non-Hodgkin lymphomas. One case each of MALT lymphoma of caecum (CD21 positive) and jejunum, one case of lymphomatous polyposis of the duodenum (CD5 and cyclin D1 positive), and one case of Mantle cell lymphoma of ileum (CD21 negative).

Introduction

Malignant lymphoid neoplasms are classified into Hodgkin's and non-Hodgkin lymphoma. Non-Hodgkin malignant lymphomas are classified into nodal and extranodal lymphomas.[1] Primary gastrointestinal Hodgkin's lymphoma is extremely uncommon. Gastrointestinal tract (GIT) is the commonest extranodal site of involvement by non-Hodgkin lymphomas. GIT lymphomas constitute 10-15% of all non-Hodgkin lymphomas and 30-40% of all extranodal lymphomas.[2]

Primary gastrointestinal lymphomas comprise a group of distinctive clinicopathological entities. They may be of B- or T-cell type. Most low grade B-cell gastrointestinal lymphomas are of mucosa-associated lymphoid tissue (MALT) type. Low grade MALT lymphomas, which usually have a very favorable clinical course, may undergo high grade transformation. High grade tumours may also arise de novo. Immunoproliferative small intestinal disease (IPSID) is a special form of MALT lymphoma with a restricted geographic distribution, and is characterized by synthesis of alpha heavy-chain immunoglobulin. Other primary gastrointestinal B-cell lymphomas include mantle cell lymphoma, which presents as lymphomatous polyposis, and Burkitt's or Burkitt-like lymphoma. Enteropathy (celiac disease)-associated T-cell lymphoma (EATL) is the most common primary gastrointestinal T-cell lymphoma, which is a clinically aggressive tumor.[1]

GI lymphomas are located more frequently in the stomach (50- 60%). Intestinal lymphomas are more infrequent and appear in the small bowel (20-30%) and the colon and rectum (10-20%).[1] Intestinal lymphomas differ from gastric lymphomas in pathology, clinical features, treatment and prognosis. The term *primary intestinal lymphoma* is defined as an extranodal lymphoma arising in the small bowel or large bowel with the bulk of the disease localized to the small/large bowel. [1]

Material and Method

A retrospective audit of primary intestinal lymphomas diagnosed at the Department of Pathology over a period of study 5 years was done. Four cases of primary intestinal lymphomas were retrieved. In each case, the relevant clinical data and investigations done was collected.

Routine 5µ paraffin sections stained with hematoxylin and eosin (H and E) were used for histopathology. Immunostaining along with appropriate positive and negative controls was performed manually on paraffin sections with the conventional avidin–biotin peroxidase technique and developed with diaminobenzidine (DAB) with pretreatment by heating in a pressure cooker in 0.01 M citrate buffer (pH 6.0). The antibodies used for IHC included CD5, CD20, CD21, Cyclin D1 (Leica). The panel of antibodies used in a given case was dependent on morphologic evaluation.

Results

Of the four cases of primary intestinal lymphomas were studied of which 3 were resected specimens and 1 endoscopic biopsy. The age of the patients ranged from 23 years to 70 years. All patients were male and all presented with pain abdomen and 2 cases also had vomiting. There was no history of ulcerative colitis, Crohn's disease or coeliac disease. Of the four cases, two cases were of MALT lymphoma (caecum and jejunum), and one case each of follicular lymphoma and lymphomatous polyposis. The clinical and morphological findings of the cases are given in Table 1.

Discussion

The incidence and localization of primary gastrointestinal lymphomas vary around the world.

The stomach is the most common site of primary GI lymphomas in Western countries, but in the Middle East most primary gastrointestinal lymphomas arise in the small intestine, followed closely by the stomach. This may be partly explained by the high prevalence of IPSID in these areas. In Western countries, gastric lymphoma predominates over intestinal lymphoma.

In a large series of GI lymphomas from South India, the intestine was involved in 43.75% of all the cases, small intestine was involved in 23.51% of the cases and colon (excluding ileocaecum & rectum) in 6.55% of the cases.[3] In a study from North India, small intestinal lymphomas were found in 71% of the primary intestinal lymphomas. [4] In another study, small and large intestines were involved in 36.36% and 16.88% of cases respectively.[5] However in two other studies the intestinal lymphomas were more frequent than gastric lymphomas.[6, 7] In this series of four cases from a centre in Mangalore, small intestine was involved in three cases and large intestine in one case.

Mucosa Associated Lymphoid Tissue (MALT) lymphoma (Figure 1) is the term given for the component of immune system that has evolved to protect the freely permeable surface of

the GIT & other mucosal membranes directly exposed to the external environment. It comprises the lymphoid nodules (which in the ileum form Peyer's patches), lymphocytes and plasma cells in the lamina propria and intraepithelial lymphocytes. Lymphomas of this tissue are called *MALT lymphomas*. [8] The cellular morphology and immunophenotype is essentially that of marginal zone B- cell. Immunophenotyping with CD 21 (Figure 2) and molecular studies for lymphoid antigen receptor gene rearrangements can be useful adjuncts in diagnosis, but should never take the place of routine histology, which remains the "gold standard" in diagnosis. [1]

Small cell lymphomas other than low grade MALT lymphomas can involve the GI tract, including Chronic Lymphocytic Lymphoma/Small Lymphocytic Lymphoma, follicular lymphoma, and, most notably *mantle cell lymphoma*. Mantle cell lymphoma (MCL) may involve any portion of the gastrointestinal tract, and this is the most common site of extranodal involvement by this tumour. Overall, between 20% and 30% of mantle cell lymphoma cases involve the GI tract, not uncommonly as the primary site of involvement. [9] MCL is an aggressive lymphoma which typically presents in advanced stage. [1]

A particularly characteristic form of GI tract involvement is the presence of multiple polypoid lesions, most commonly in the ileocaecal region, a condition termed *multiple lymphomatous polyposis*. [1, 9] Multiple lymphomatous polyposis (Figure 3) primarily affects male patients with median age 61 years. Its prevalence is uncommon (3 % - 9%). Most cases are mantle cell lymphoma. MALT lymphoma has also been reported to present as lymphomatous polyposis in the colon. A rare case of primary T-cell lymphoma resembling lymphomatous polyposis has been reported in literature. [8]

Mantle cell lymphoma shows a variety of immunophenotypic characteristics which can be quite useful in arriving at the correct diagnosis. By immunophenotyping, the cells appear as B-cells with immunoglobulin light chain restriction which are CD5 positive and CD23 negative, an immunophenotype virtually diagnostic of mantle cell lymphoma. In addition, cyclin D1 overexpression can be detected. [9]

Follicular Lymphoma is a neoplasm composed of follicle center (germinal center) B cells, both centrocytes and centroblasts which usually have a partially follicular pattern. They are defined by CD21/CD23 positivity. [10]

Primary follicular lymphomas (PFL) of the gastrointestinal tract are very rare and constitute <7% of all non-Hodgkin's lymphomas at this location. They have a predilection to the ileum. Primary intestinal follicular lymphoma is more common in 2nd part of duodenum. PFL on endoscopy can resemble multiple lymphomatous polyposis. These findings are important clinically, since mantle cell lymphoma has a poor prognosis and requires aggressive first-line high-dose therapy. Therefore, immunostaining for CD5, CD 20, CD21 and cyclin D1was done in order to differentiate between a diagnosis of lymphomatous polyposis and that of PFL. [10]

With regard to the prognostic factors for primary small intestine lymphoma, one study has performed a multivariate analysis of small intestine lymphoma cases (excluding primary gastric or colorectal lymphomas). They found clinical stage, perforation, histologic grade, and location in the terminal ileum to be independent prognostic factors. [1]

In conclusion, intestinal lymphomas are rare. They are more common in the older age group and in males. The commonest site is the small intestine with MALT lymphomas being predominant.

Table 1 Clinical and Morphological Features

FEATURE	CASE 1	CASE 2	CASE 3	CASE 4
Age (years)	70	23	60	61
Sex	Male	Male	Male	Male
Site	Caecum	Jejunum	Duodenum	Ileum
Clinical presentation	Pain abdomen, Vomiting	Pain abdomen, Vomiting,	Pain abdomen	Pain abdomen
Radiological findings	CT abdomen Circumferential bowel wall thickening of ileocaecal region predominantly involving the caecum.	CT abdomen Exophytic growth noted in the jejunum	GI endoscopy Polyps seen in the duodenum	Not available
Microscopic findings	Centrocyte – like cells, mature lymphocytes and monocytoid cells with clear cytoplasm. Plasma cell differentiation with Dutcher bodies. Lymphoepithelial lesions.	Neoplastic lymphocytes of small cleaved type infiltrating the entire wall. Lymphoepithelial lesions seen.	Diffuse infiltration of entire wall by round to oval cells which are small lymphocytes with irregular to deeply clefted nuclear contours with scanty cytoplasm.	Diffuse infiltration of entire wall by small irregular cleaved cells (centrocytes) with scanty cytoplasm. Few centroblasts are also seen.
Histopathologic diagnosis	MALT lymphoma	MALT lymphoma	Multiple lymphomatous polyposis (Mantle cell lymphoma)	Follicular lymphoma
IHC done	CD 20 & CD 21 POSITIVE	Not done	CYCLIN D1 & CD5 POSITIVE	CD 20 POSITIVE CD5, CYCLIN D1 & CD 21 NEGATIVE

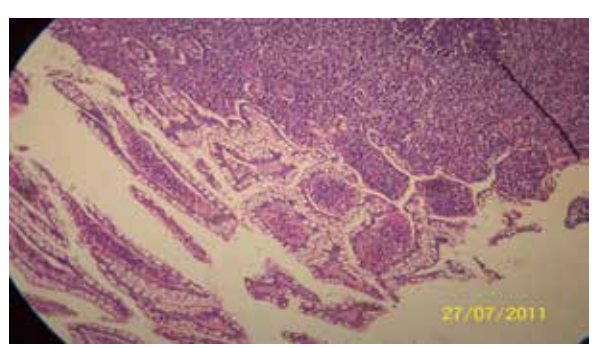

Figure 1: MALT Lymphoma of Ceacum: colonic mucosa with dense infiltrate dyscohesive, polymorphic cells and lymphoepithelial lesions (H and E stain; ×10 magnification)

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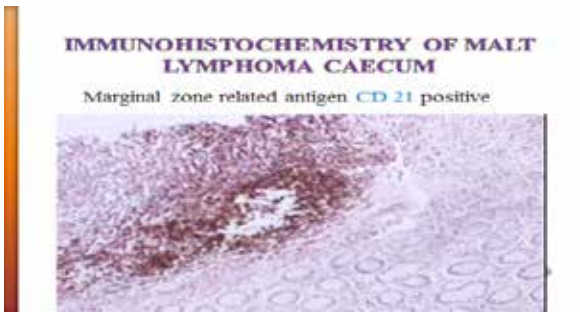

Figure 2: Marginal zone related antigen CD21 positive; ×10 magnification

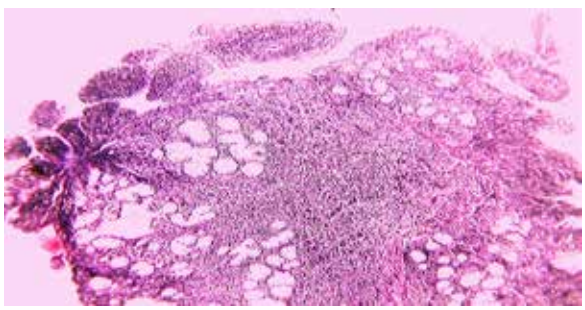

Figure 3: Lymphomatoid Polyposis: showing diffuse infiltration by small lymphocytes (H and E stain; ×10 magnification)

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