Gastro

GASTROINTESTINAL LYMPHOMA

MEDICAL GRAND ROUNDS
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Hodgkin's original description of malignant transformation of the lymph nodes appeared more than 150 years ago (1). The precise nature of the transformed cell in Hodgkin's disease is still debated, although current evidence points to a macrophage derivation. More importantly, significant advances have occurred in Hodgkin's disease in terms of classification, a more precise staging and selection of treatment according to the stage. Similarly, more powerful chemotherapeutic agents have been developed, and the radiotherapy has been refined. These advances are reflected in significantly improved survival rates in patients with Hodgkin's disease.

Over the years it became apparent that lymph nodes and lymphoid tissue may undergo malignant transformation without histologic evidence of Hodgkin's disease, and thus the non-Hodgkin's lymphomas (NHL) became established as disease entities. Billroth, a famous gastrointestinal surgeon, is credited with the first description of a case of a gastrointestinal lymphoma (2). The presentation today will focus on primary non-Hodgkin's lymphomas of the gastrointestinal tract. Gastrointestinal involvement in Hodgkin's disease is rare, even in advanced stages, and will not be discussed. Primary gastrointestinal lymphoma was originally defined by Dawson and Morson (3) as lymphomas which at presentation appeared to originate from the gastrointestinal tract without involvement of distant lymph nodes, liver or spleen. As will become obvious later on, the definition includes only patients with early stage disease. In more widespread disease, it is often not possible to determine the primary origin of the lymphoma. The definition has, however, been used in most series of gastrointestinal lymphomas. It should be stated from the outset that primary gastrointestinal lymphomas are rare, and in large series comprise only 1-2% of all gastrointestinal malignancies (4). The review will focus on a number of interesting and controversial issues in primary gastrointestinal lymphomas:

1. Do gastrointestinal lymphomas originate from a distinct population of cells in the mucosa-associated lymphoid tissue, and are these lymphomas a distinct subgroup within the spectrum of non-Hodgkin's lymphomas?

2. The staging and classification systems currently in use in non-Hodgkin's lymphomas.

3. The association of small intestinal lymphoma with certain geographic areas and specific diseases.

4. The role of surgery, radiotherapy and chemotherapy in the treatment.

Mucosa-associated Lymphoid Tissue (MALT)

The lymphoid tissue of the gastrointestinal tract form a distinct compartment of the peripheral lymphoid system (5). The lymphoid tissue is organized in solitary lymphoid follicles in the submucosa throughout the gastrointestinal tract. Aggregates of lymphoid follicles form the Peyer's patches which are from 2 to 10 cm in length and are located on the antimesenterial border of the intestine. There are about 200 Peyer's patches in the human intestine, and they occur with the highest density in the ileocecal region. Lymphoid cells appear in the intestine in fetal life, but distinct lymphoid follicles are not found until the first week after birth.

Germinal centers develop within the first month. The development of germinal centers is dependent on environmental antigens, and germinal centers do not develop in mice brought in an antigen-free (axenic) environment (6). Similarly, if a segment of the intestine is excluded at birth, the Peyer's patches in this segment develop only to about one-tenth of the size of the patches in the normal intestine and germinal centers are not seen (7). Thus, the exposure to environmental antigens which commences at birth is a determinant factor in the final development of the lymphoid tissue in the intestine. It has been estimated that the mass of lymphoid tissue in the intestine is equivalent to the mass of the spleen. The structure of the Peyer's patches is illustrated schematically in Fig. 1.

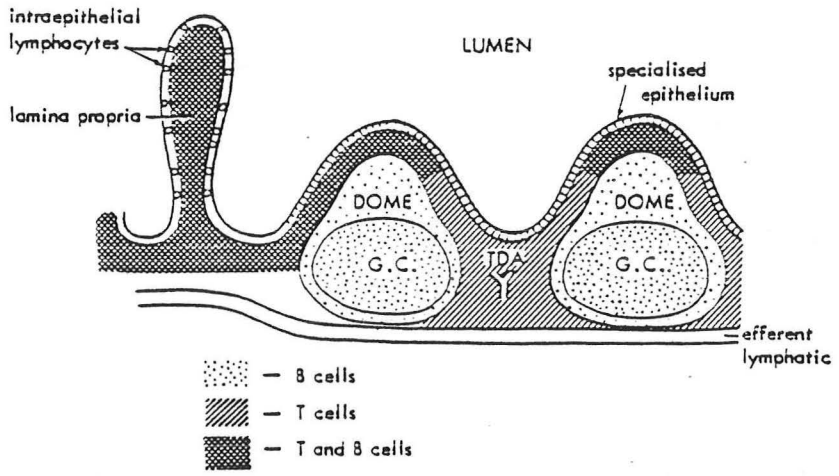

Fig. 1 - Diagram of a Peyer's Patch

The picture shows two solitary follicles or germinal centers (GC) which are almost exclusively composed of follicle center cells (centroblasts or centrocytes) which are thought to be virgin B cells. The precise placement of follicle center cells in the ontogeny of B cells is not well-defined at this time. Above the follicles is the dome area which faces the gut lumen between the intestinal villi. The dome area is occupied by B cells (centrocyte-like cells), T cells, macrophages and mast cells. The epithelium over the dome area is composed of cuboidal cells rather than the columnar cells on the villi. Among the cuboidal cells are also found a specialized cell type, the M cells, which are important in antigen presentation to the follicle (8). The area between the follicles is occupied by mostly T cells, which are in traffic to the lamina propria and the mucosa.

The gut is continuously exposed to a number of ingested antigens which may be taken up into the solitary follicles through the dome epithelium by pinocytosis by the M cells. Once transported through the M cells the antigen is presented to macrophages in the dome area and further processed in the lymphoid follicles where a series of events are initiated. The antigen is presented to helper T cells (T4) and through the actions of soluble factors (interleukin 1 and 2) these T cells proliferate and induce immature surface IgM bearing B cells to switch to IgA synthesis (9). The switched B cells are

induced to proliferate and differentiate through the action of maturation factors secreted from other T cell types. The antigen-activated T cells also undergo proliferation and differentation in a pattern similar to the B cells.

Although the primary interaction between antigen and the antigen processing cells takes place in the solitary follicle, a direct immune response is not elicited here. The number of antibody producing cells (plasma cells) in the follicles is very low. Less than 2% of the cells in the follicle centers contain surface IgA (S-IgA). The response to the antigens (proliferation and differentation) starts within the follicle, but the primed cells then leave via the efferent lymphatics and pass to the mesenteric lymph nodes and further on to the systemic circulation. The B-immunoblasts differentiate into IgA secreting plasma cells during this passage. The most interesting feature of these activated cells is that they return to the intestine and take residence in the lamina propria of the gut, which is heavily infiltrated by these cells. More than 90% of the plasma cells in the lamina propria contain surface IgA (10). Similarly, activated T cells also return to the lamina propria and to the mucosa as intraepithelial lymphocytes.

The T lymphocytes in the lamina propria consist of helper (T4) and suppressor cells (T8), lymphokine-activated killer cells and natural killer cells (11). The intraepithelial lymphocytes are mainly natural killer cells and suppressor cells (12). B cells are not found among the absorptive epithelial cells. The intraepithelial T cells have cytotoxic function especially against cells infected with enteroviruses (13). Thus, an attack on ingested antigens can be initiated by the intraepithelial lymphocytes. Antigens that escape the initial attack and arrive in the lamina propria may be defeated by several types of inflammatory responses elicited by the lamina propria lymphocytes.

The antigen-activated T and B cells home in on the intestine within hours. In a time course experiment it was found that radioactive labelled activated mesenteric lymph node cells were found in the lamina propria within one hour and after 24 hours more than 60% of the total radioactivity was recovered in the small intestine (5). Antigen-activated lymphocytes from a peripheral lymph node on the other hand do not home to the gut (10). The peculiar recirculation of the activated cells from the Peyer's patches to the lamina propria is illustrated schematically in Fig. 2.

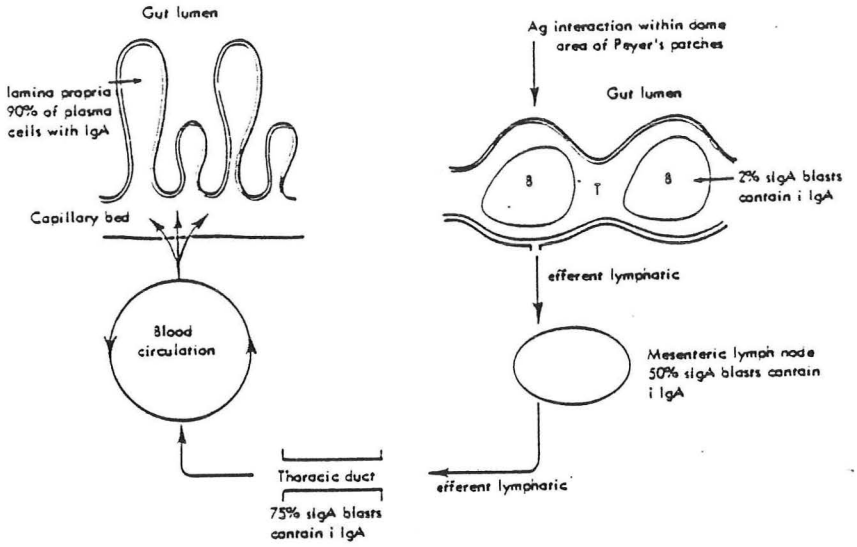

Fig. 2 - Maturation Journey of Blast-Transformed Follicle Center Cells (5)

At present the signals which induce the activated B and T cells to return to the intestine are unknown.

The secretion of IgA from the dominant fraction of plasma cells in the lamina propria constitutes another arm of the immune defense in the gastrointestinal tract. The secretory IgA consists of two IgA molecules hold together by a polypeptide chain (J-chain-joining segment) as shown in Fig. 3.

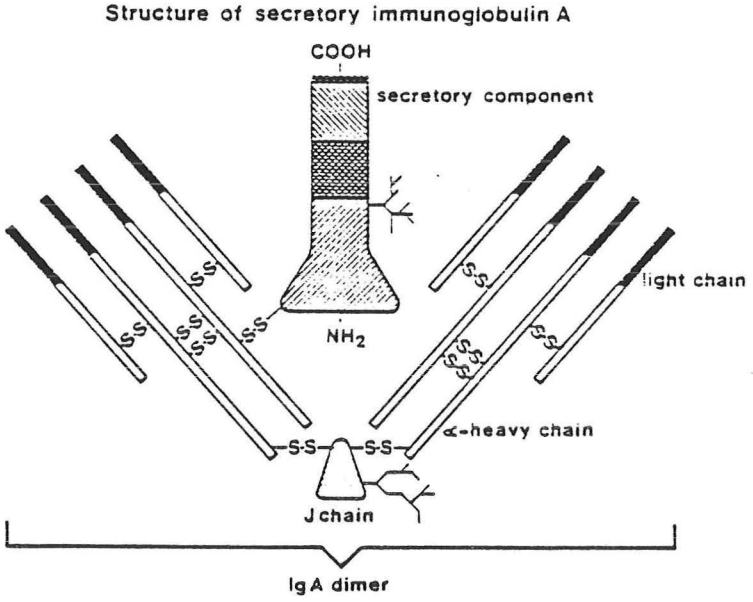

Fig. 3

The dimeric IgA and the J-chain are synthesized in the plasma cells and diffuses up to the basolateral membrane where it attaches to the secretory component of the epithelial cells (14). The secretory component is synthesized in the epithelial cells and inserted in the cell membrane as a transmembrane protein. After the attachment, secretory IgA is taken up into the cell by receptor-mediated endocytosis, and the endocytic vesicle moves to the apical membrane where it fuses with the cell membrane and secretory IgA is released to the gut lumen. The secretory IgA functions as a blocking antibody by binding to viruses, bacteria or macromolecules. The antigen-antibody complex remains in the gut lumen and prevents antigen activation of the mucosa-associated lymphoid tissue.

One characteristic feature of primary gastrointestinal lymphomas is that they may remain as localized disease for a prolonged period of time. One reason for this behavior may be that the neoplastic cells from a lymphoma return to the gut similar to the activated nonneoplastic cells. Isaacson and Spencer (15) have recently argued that the centrocyte-like cells may belong to a distinct B cell lineage which form a noncirculating compartment analogous to the splenic marginal zone cells which also would explain that the lymphoma remains localized.

Incidence

The true incidence of primary gastrointestinal lymphoma is difficult to ascertain. Most of the larger series on gastrointestinal lymphoma come from large referral centers, and thus do not reflect the number of new cases within a defined population. Two smaller series come from hospitals which serve as the sole referral center for a defined population in Scotland and Sweden, respectively (16,17). The calculated incidence from these two series corresponds to 1.5 cases/100.000 adults/year.

There is general agreement among the several large series of primary gastrointestinal lymphoma that gastric lymphoma is more frequent than small intestinal lymphoma which again is more frequent than colonic lymphoma. The actual frequency of lymphoma at these three sites is shown in Table 1,

TABLE 1
THE FREQUENCY OF GASTRIC, SMALL INTESTINAL AND COLONIC PRIMARY LYMPHOMA

	Stomach	Small Intestine	Colon	Total
Saraga (18)	55	28	18	101
Weingrad (19)	76	15	13	104
Fillipa (20)	45	4	11	60
Isaacson (21)	24	32	10	66
Contreary (22)	67	24	21	112
Rosenfelt (23)	27	8	3	38
Lewin (24)	48	37	26	111
Aozasa (25)	67	31	3	101
Dragosics (26)	105	18	10	133
Papadimitriou (27)	39	15	7	61
TOTAL	553	212	122	887
% of Total	62	24	14	

which comprises data from 10 large, retrospective series totalling 887 patients. It should be emphasized that these 10 studies are all from Western countries and the frequency rates cannot be extrapolated to Eastern (or less developed) countries where small intestinal lymphoma is the most frequent lesion (28).

The age-related incidence for adult primary gastrointestinal lymphoma shows the highest frequency in the sixth and seventh decade as shown in Fig. 4.

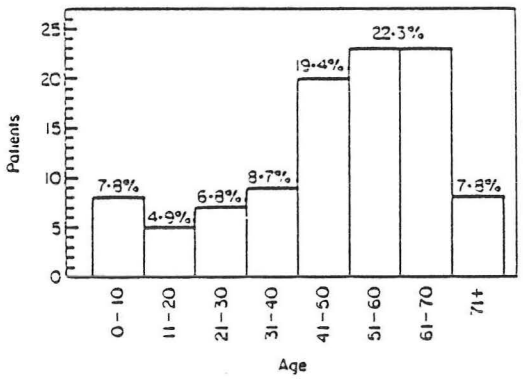

Fig. 4 - Age-related Incidence in 104 Cases of Primary Gastrointestinal Lymphoma (29)

The figure also shows a small peak in the age group 0 to 10 years. The childhood lymphomas which include Burkitt's lymphoma will not be discussed in this presentation.

Staging of primary gastrointestinal lymphoma

The staging classification of non-Hodgkin's lymphoma was defined at a conference in Ann Arbor in 1971 and is very similar to the staging of Hodgkin's disease (30). The Ann Arbor staging classification system is outlined in Table 2.

TABLE 2 - ANN ARBOR STAGING CLASSIFICATION

I.	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE).
II.	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphagm (IIE).
III.	Involvement of lymph node regions on both sides of the diaphragm and/or localized involvement of extralymphatic organs.
IV.	Diffuse involvement of one or more extralymphatic organs or tissues with or without lymph node involvement.

The letter E denotes extranodal disease, and primary gastrointestinal lymphomas are thus by definition staged into IE and IIE. As stated previously, it is often difficult to determine the primary site of origin of the lymphoma in stage III and IV when the patient presents in these stages. Stage IIE disease may be further subdivided into IIE_1 with involvement of contiguous lymph nodes and IIE_2 with involvement of regional but noncontiguous lymph nodes (31).

The procedures used in staging of non-Hodgkins lymphoma follow the guidelines outlined for Hodgkin's disease and should include a detailed history and physical examination, standard laboratory tests including liver function tests, chest x-ray, lymphangiogram, and CT scan of the abdomen. Further procedures may include bone marrow biopsy and liver biopsy (32). In primary gastrointestinal lymphomas where the presenting symptoms often are GI related, the workup should involve upper GI with SBFT, barium enema and endoscopy/colonoscopy with biopsies if a lesion has been demonstrated on the barium studies. In lymphomas involving the proximal small intestine small bowel biopsy should be performed.

Staging laparotomy is generally not recommended in NHL. The major purpose of staging is to determine whether the patient has limited nodal or extranodal disease (stage I and II) or disseminated disease (stages III and IV) and thus to select treatment according to the stage. Patients with primary gastrointestinal lymphoma will, however, often require surgery either

because they present with symptoms of an abdominal emergency or for the acquisition of adequate tissue for diagnosis. It should also be emphasized that surgery has a definite role as a therapeutic approach to patients with stage IE and IIE disease as will be discussed later.

The Ann Arbor staging classification has proven its value in Hodgkin disease in that prognosis is related to stage. It has been claimed that the staging system has a more limited value in non-Hodgkin's lymphomas and that the prognosis correlates less well with the stage in these diseases (32).

Histologic classification of NHL

The histologic classification of non-Hodgkin's lymphomas has been a controversial issue and several classification schemes have been formulated over the last two decades to try to resolve the controversy (33). There are currently four major classification schemes in use, and they will be briefly summarized in this section.

The first and most simple classification was proposed by Rappaport in 1966 (34) and is based on three morphologic features: 1) architecture of the lymphoma (nodular or diffuse pattern), 2) histologic cell type (lymphocytic or histocytic) and 3) the degree of differentiation as shown in Table 3.

TABLE 3 - RAPPAPORT'S CLASSIFICATION

Cell Type	Growth Pattern
Lymphocytic	
Well-differentiated	Diffuse or nodular
Poorly differentiated	
Histiocytic	Diffuse or nodular
Mixed cell	
Histiocytic and lymphocytic	Nodular

Rappaport's classification has been widely used because it is relatively simple and reproducible among different pathologists. It has also been found that the prognosis is determined to a certain degree by the morphology of the lymphoma. Nodular and well-differentiated lymphomas have a better prognosis than diffuse and poorly differentiated lymphomas. The major shortcoming of Rappaport's classification is the term histiocytic lymphoma. The cells classified as histiocytes by Rappaport are, in fact, not histiocytes but follicle center cells, i.e., primitive B cells. True histiocytic tumors are very rare (<1%) among non-Hodgkin's lymphomas (35).

In 1974 Lukes and Collins proposed a new classification of NHL. They compared the morphology of the cells in the solitary follicles and lymph nodes with the cells observed in nodular lymphoma (36). The primary cell types of a lymphoid follicle are follicle center cells (FCC), which may be subdivided into small cleaved cells (cleaved nucleus) and larger noncleaved and cleaved

cells, lymphocytes and macrophages, and the same cell types may be observed in nodular lymphomas.

TABLE 4 - LUKES AND COLLINS CLASSIFICATION

Cell Type
FCC, Small, cleaved
FCC, Large, cleaved
FCC, Large, Noncleaved
Plasmacytoid
Immunoblastic
Lymphocytic

Lukes and Collins classification does not include histiocytic lymphoma, which was not considered to be a true lymphoma. They also emphasized that all non-Hodgkin's lymphoma are derived from B and T lymphocyte stem cells. There is only limited clinical experience with Lukes and Collins classification, and the morphologic classification of the different cell types is difficult.

In 1975 Lennert from Kiel, West Germany, proposed another classification which divides the lymphomas in two major subgroups: low grade and high grade malignancy as shown in Table 5 (37).

TABLE 5 - KIEL CLASSIFICATION

	Cell Type
Low grade	Centroblastic/centrocytic
	Centrocytic
	Lymphocytic
	Immunocytic
High grade	Centroblastic
	Lymphoblastic
	Immunoblastic

The centrocytic lymphomas correspond to the small cleaved FCC of Lukes and Collins and the centroblastic/centrocytic cells correspond to the large cleaved cells. Both are B cell tumors and grow in a nodular pattern. The immunoblastic cells of Lukes and Collins and Kiel classification correspond to the histiocytic lymphoma of Rappaport. As with the Lukes and Collins scheme, the Kiel classification has not gained widespread acceptance due to the complexity of the nomenclature and problems with the practical application. It should also be noted that the Kiel scheme ignores the pattern of tumor (nodular or diffuse).

It is apparent that none of the classification systems are entirely satisfactory and the need for a more accurate, convenient and consistent classification was emphasized. Recently, a panel of experts have agreed on a new working formulation of NHL (38). The proposed classification scheme is shown in Table 6 together with the Rappaport equivalent.

TABLE 6

A WORKING FORMULATION OF NON-HODGKIN'S LYMPHOMA FOR CLINICAL USE: RECOMMENDATIONS OF AN EXPERT INTERNATIONAL PANEL

International formulation	*Rappaport equivalent*
Low Grade	
Small lymphocytic	Well differentiated lymphocytic
consistent with chronic lymphocytic leukemia	tissue manifestation of chronic lymphocytic leukemia
plasmacytoid	with plasmacytoid features
Follicular— predominantly small cleaved cell	Nodular poorly differentiated lymphocytic
Follicular— mixed small cleaved and large cell	Nodular mixed
Intermediate Grade	
Follicular predominantly large cell	Nodular histiocytic
Diffuse small cleaved	Diffuse poorly differentiated lymphocytic
Diffuse mixed small and large cell	Diffuse mixed
epithelioid cell component	
Diffuse large cell	Diffuse histiocytic lymphoma
cleaved	
noncleaved	
High Grade	
Diffuse large cell immunoblastic	Immunoblastic
plasmacytoid	
clear cell	
polymorphous	
epithelioid cell	
Lymphoblastic	Lymphoblastic
convoluted	
nonconvoluted	
Small noncleaved cell	Diffuse undifferentiated
Burkitt's	Burkitt's
follicular areas	
Miscellaneous	
Composite	Composite
Mycosis fungoides	Mycosis fungoides
Histiocytic	Histiocytic
Extramedullary	Extramedullary
Unclassifiable	Unclassifiable
Other	Other

It is immediately recognized that the scheme is even more complex and now includes three subgroups: low grade, intermediate grade and high grade

malignancy. The new classification system has only been used in a few large series of primary gastrointestinal lymphomas (26,39). In a recent review of 133 cases of gastrointestinal NHL (26), it was found that classification by any of the four systems had only a minor influence on prognosis contrary to previous observations (19). A similar conclusion was reached in a study from France where it was found that the working formulation classification had a good prognostic value in NHL of the lymph nodes but failed to reveal any predictive value for primary gastrointestinal lymphoma (40).

It is therefore apparent that an ideal classification system remains to be defined. The advent and increasing use of monoclonal antibodies to define cell surface markers may help to elucidate the phenotypic characteristics of the tumor cells and may also provide means to establish a new classification system.

Gastric lymphoma

Case 1: A 35-year-old white male who has a two-year history of burning epigastric pain accompanied by a 20 pound weight loss. An upper GI in 1985 at another hospital had shown a gastric ulcer. Treatment with H_2-blockers and antacids had resulted in moderate symptomatic relief. He was first seen at the VAMC in November of 1986 because of increasing symptoms. He was a heavy smoker and used NSAIDs for pain relief. Endoscopy showed three gastric ulcers on the lesser curvature with a benign appearance. Biopsies demonstrated nonspecific inflammation. NSAIDs were discontinued and treatment with Tagamet and antacids was reinstituted. Reendoscopy in December of 1986 showed that the ulcers were smaller and appeared healing. Biopsies were again negative. He remained symptomatic and underwent a third endoscopy in February of 1987 which showed that the three ulcers were still present. Biopsies were now interpreted as showing atypia. He was taken to surgery and underwent an antrectomy and vagotomy. Histologic examination of the ulcers showed lymphoma. He subsequently underwent a subtotal gastrectomy. There was no evidence of lymphoma in the resected specimen or in the lymph nodes.

Presenting symptoms

The case described above is a typical presentation for a primary gastric lymphoma. It further illustrates that the patients may be symptomatic for several years and that the gastric lesion is often misrecognized as a benign gastric ulcer. The clinical symptoms in gastric lymphoma are listed in Table 7.

TABLE 7
CLINICAL SYMPTOMS IN 56 PATIENTS WITH GASTRIC LYMPHOMA (41)

Pain	78%
Weight loss	40%
Vomiting	32%
Bleeding	20%
Nausea	14%
Anorexia	10%
Weakness	4%
Night sweats	2%
Asymptomatic	0%

It is evident that the symptomatology is suggestive of peptic ulcer disease. The findings on an upper GI series are abnormal in most cases. In the series listed in Table 7, upper GI was abnormal in all cases demonstrating either a mass lesion or an ulcer. In a smaller, more recent series where endoscopy was included in the workup, the endoscopic findings were abnormal in all 12 cases with a mass lesion in 2, an ulcer in 7 and gastritis as the only abnormal finding in 3 patients (42). The endoscopic findings suggest that early lesions in primary gastric lymphoma present as gastritis which subsequently may develop into an ulcer or a mass lesion. It also underscores the need for endoscopic biopsies in symptomatic patients with gastritis.

Classification of primary gastric lymphoma

The 553 cases of primary gastric lymphomas listed in Table 1 are all from retrospective series collected over a long period of time from 20 to 30 years. As outlined previously, the classification systems have undergone significant changes within the last 20 years which is reflected in these retrospective series by the use of different systems. It is therefore difficult to compare these series due to classification differences. It is apparent though that large cell lymphomas (diffuse histiocytic (Rappaport)) predominate and account for 50 to 70% of all primary gastric lymphomas (4,33). In a more recent study of 36 gastric lymphoma collected from 1975 to 1982 and classified with the Kiel system, all 36 lymphomas were categorized as follicle center cell lymphoma which suggests a B cell origin (43). The distribution of the 36 lymphomas among the various subtypes of the Kiel system is shown in Table 8.

TABLE 8 - CLASSIFICATION OF 36 CASES OF GASTRIC LYMPHOMA (43)

Type of follicle centre cell lymphoma	Pattern of infiltration	No. of cases
Centroblastic/ centrocytic with plasmacytic differentiation	Follicular & diffuse	3
	Diffuse	1
		4
Centroblastic/ centrocytic	Follicular & diffuse	3
	Follicular	1
	Diffuse	4
	Impossible to assess	6
		14
Centroblastic	Follicular & diffuse	2
	Diffuse	9
		11
Centrocytic	Diffuse	7

The microscopic features of a typical lymphoma lesion demonstrate intense invasion of the lamina propria with plasma cells and follicle center cells in the deeper layers of the lamina propria arranged as follicular (nodular) or diffuse infiltrates. A characteristic feature of the neoplastic FCCs is that they invade the gastric glands forming a so-called lymphoepithelial lesion which the authors considered a pathognomonic lesion of primary gastric lymphoma (43). All the specimens reviewed in this study were paraffin embedded and formalin fixed. The fixation process partially destroys the surface immunoglobulins and often precludes further immunologic characterization of the cell phenotypes. Only in one case was frozen tissue available and in this case the immunologic phenotype of the FCCs was found to be identical to that of the invading plasma cells. In a series of 25 gastrointestinal lymphomas from Stanford, which included 17 primary gastric lymphomas, only frozen tissue was used for immunologic characterization (44). Twelve of the 17 cases were found to be B cells by monoclonal staining for surface light and heavy immunoglobulin chains; 3 were of B cell lineage as they stained positive with a B cell lineage marker (B1). Finally, two cases were undefined but stained positive with two panleukocyte markers (T200 and L3B12). These observations were recently extended by Isaacson (42) in a study of 12 cases of primary gastric lymphoma where frozen tissue was available in all cases. Fourteen monoclonal antibodies were used to characterize the neoplastic cells. In each case the characteristic lymphoepithelial lesion was demonstrated, and the FCCs and centrocyte-like cells were shown to express monoclonal surface immunoglobulins of the same isotype. Furthermore, the neoplastic FCCs were found to stain positive with two antibodies for proliferating, activated B cells (MHM6, Ki67) whereas the neoplastic centrocyte-like cells stained as resting B cells (KB61). These two studies

have convincingly demonstrated that the neoplastic cells in primary gastric lymphoma are derived from B cells. The presence of a monoclonal (light-chain restricted) B cell infiltrate is thought to be synonymous with lymphoma and argues for the use of frozen tissue specimens to establish the diagnosis. The use of a panel of monoclonal antibodies to characterize the phenotype of the neoplastic cells may also aid in the classification of non-Hodgkin's lymphomas.

Pseudolymphoma

The two most important differential diganoses to be considered in gastric lymphoma are adenocarcinoma and pseudolymphoma. The term pseudolymphoma was introduced by Jacobs (45) to describe a benign lymphoid lesion which often occurs in association with a benign gastric ulcer. Pseudolymphoma accounts for 6-15% of all lymphoid lesions in the stomach (46). The diagnosis of a pseudolymphoma usually requires a full thickness tissue specimen obtained at gastric resection. The criteria for the presence of a pseudolymphoma is the finding of lymphoid follicles with germinal centers at all levels within the lesion and associated with a dense lymphocytic infiltrate. Furthermore, lymphoepithelial lesions and infiltration with FCCs between the follicles must be absent because these two features would favor a diagnosis of lymphoma. Staining for surface immunoglobulin markers with monoclonal antibodies is particularly helpful in the distinction between lymphoma and pseudolymphoma in that lymphomas will demonstrate a monoclonal cell population whereas the infiltrating cells in pseudolymphoma are polyclonal. Similarly, the distinction between lymphoma and anaplastic adenocarcinoma may be resolved with the use of epithelial cell markers (cytokeratin, CEA). It should be emphasized that pseudolymphoma should be regarded as a premalignant condition. Several reports have described the transition from pseudolymphoma to lymphoma (47,48). Isaacson has recently argued that the term pseudolymphoma should no longer be used and instead suggests the term "reactive lymphoid infiltrates" (42). The current histologic techniques should allow the distinction between lymphoma and reactive lymphoid infiltrates according to the criteria outlined in Table 9.

TABLE 9 - CRITERIA FOR THE DIAGNOSIS OF GASTRIC LYMPHOMA (42)

	Lymphoma	Reactive Lymphoid Infiltrates
Follicles	±	+
Centrocyte-like cells	+	-
Lymphoepithelial lesions	+	-
Plasma cells	+	+

Treatment

The treatment of primary gastric lymphoma has undergone major changes over the last three decades. In the early series the diagnosis of gastric lymphoma was often an unexpected finding at laparotomy, and the treatment consisted of partial or total gastrectomy with or without radiotherapy depending on the stage at presentation. Later on chemotherapy was added as a treatment modality, first as a single agent and later as combination chemotherapy. The large retrospective reviews of primary gastric lymphoma often cover up to 30 years, and the treatment offered to the patients in these series reflects the continuous development of new and more aggressive treatment plans (49-54). Furthermore, a significant proportion of the patients were treated before formal staging and classification systems were formulated and thus were staged and classified retrospectively from the data available at the time of analysis. The inherent inaccuracies in retrospective staging are readily appreciated. With these reservations in mind, it is apparent that these retrospective series only offer limited information. Despite the inhomogeneity of the treatment modalities and differences in classification in these series, there was general agreement on the following points.

First, the five-year survival is related to stage at presentation, tumor size and depth of penetration of the lesion. For instance, in one series of 112 cases of primary gastric lymphoma (stage IE and IIE) the five-year survival rate was 62% for stage IE, 50% for stage IIE_1 and only 25% for stage IIE_2, respectively (50). The survival curves for this series is illustrated in Fig. 5. A larger tumor size was similarly associated with a poorer prognosis (Fig. 6).

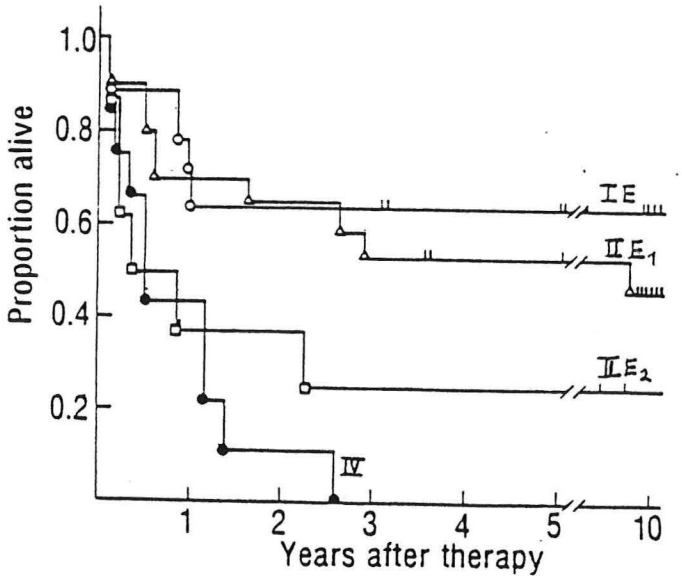

Fig. 5

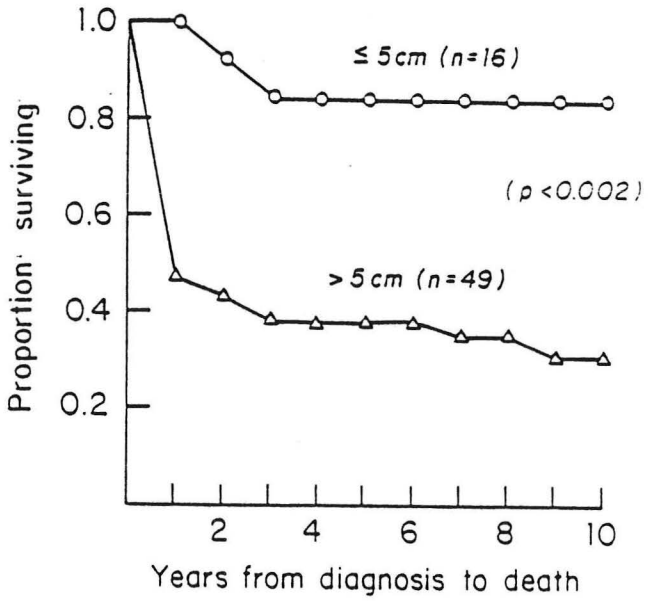

Fig. 6

Second, radical surgery favored a better prognosis than incomplete resection. The feasibility of radical surgery is, of course, mainly a reflection of stage in that attempts of complete resection are more readily accomplished in stage IE than in more advanced stages.

There was disagreement, however, among these series whether histologic classification was of prognostic value and whether the addition of radiotherapy or chemotherapy to surgery improved survival. In some series, however, improved survival was observed with more intense radiotherapy or chemotherapy (52).

Thus, the role of surgery, radiotherapy and chemotherapy in the early stages (IE and IIE) of primary gastric lymphoma remained undefined from these series. Some answers to these questions have, however, emerged from a recent report from this institution (55). In this study, thirty-three consecutive patients with large cell (histiocytic) lymphoma of the stomach seen from 1974 to 1980 were reviewed. All patients underwent surgical exploration with gastric resection, either complete or incomplete, depending on the feasibility of radical resection. The distribution of the 33 patients according to stage, resectability and lymphoma-free survival is shown in Table 10.

TABLE 10

Lymphoma-Free Survival Relative to the Extent of Surgical Resection

Extent of Resection	Status of Patients: Lymphoma Free	Status of Patients: Death due to Lymphoma	Total
Stage IE			
Complete resection	7	0	7
Stage IIE			
Complete resection	8	3	11
Incomplete resection	1	6	7
Stage IV			
Complete resection	4	0	4
Incomplete resection	0	4	4
Total	20	13	33

In the postoperative phase the patients received either no further treatment, radiotherapy or chemotherapy as shown in Table 11.

TABLE 11

Lymphoma-Free Survival Relative to the Mode of Initial Therapy Following Surgery

Postsurgical Management*	Surgical Therapy	
	Resection	Incomplete Resection
Stage IE		
No Rx	2/2	0
RT	2/2	0
Chemo	3/3	0
Stage IIE		
No Rx	0/2	0
RT	2/3	0/3
Chemo	6/6	1/4
Stage IV		
Chemo	4/4	0/4

*No Rx, no therapy; Chemo, chemotherapy; RT, radiotherapy.

Of the seven patients with stage IE disease, who all had complete resection, all survived irrespective of the postoperative treatment. Eleven patients with stage IIE had complete resection of which 6 of 6 treated with chemotherapy and 2 of 3 treated with radiotherapy remained lymphoma free. Two patients with complete resection received no further treatment, and both died of recurrent lymphoma. Of the 7 patients with stage IIE and incomplete resection, 3 were treated with radiotherapy and none survived. Only one out of four treated with chemotherapy remained lymphoma free. All eight patients with stage IV disease received chemotherapy. Four had a complete resection, and all remained lymphoma free. The four patients who had incomplete resection died of progressive disease. The authors concluded that 1) radical resection, if possible, should be performed prior to chemo- or radiotherapy; 2) systemic chemotherapy is recommended for stage IIE disease and 3) radical resection alone may be sufficient for stage IE. A prospective randomized trial was recommended to answer these questions.

So far there is only one prospective trial of combined surgery and chemotherapy in primary gastric lymphoma. In this trial from Australia, twenty-three consecutive patients were entered into the study from 1974 to 1983 (56). Eighteen patients had a complete resection of the primary gastric lesion (group A) while five patients had incomplete resections (group B). In group A ten patients had stage IE disease and were treated with cyclophosphamide, vincristine and prednisolone (CVP). Eight patients with stage IIE and IV received cyclophosphamide, doxorubicin vincristine and prednisolone (CHOP). Chemotherapy was continued for two courses after complete remission. There was one postoperative death not related to the lymphoma in group A. All 17 remaining patients are alive and disease free at follow up ranging from 5 to 111 months (median follow up: 41 months). Of the 5 patients in group B, 2 received no chemotherapy due to severe preexisting medical conditions, and both died of progressive lymphoma. One patient

developed massive hematemesis and died after initiation of chemotherapy. The remaining 2 patients are alive and lymphoma free. This small study confirms the value of radical resection and aggressive chemotherapy. The promising results need to be confirmed by a large series of patients which can only be accomplished by a randomized multicenter trial before the optimal treatment of the various stages of primary gastric lymphoma can be established.

Finally, it should be noted that the more aggressive treatment modalities are not without risks. The rapid lysis of tumor cells induced by radiotherapy or chemotherapy is associated with an increased risk of bleeding or perforation (57). In a series of 36 patients with gastrointestinal lymphoma treated with surgery, radiotherapy and chemotherapy 18 patients (50%) died due to either perforation or bleeding (58).

Small intestinal lymphoma

Malignant tumors of the small intestine are exceedingly rare and account for only 3 to 6 percent of all malignancies in the gastrointestinal tract (59). In Western countries, lymphoma accounts for about 20% of neoplastic tumors of the small intestine. In the Middle East, however, small intestinal lymphoma is the most common of all intestinal malignancies. It has been claimed that Western and Eastern intestinal lymphoma are distinct entities, and they will therefore be considered separately.

Western lymphoma

The age at presentation is similar to gastric lymphoma with the highest incidence in the sixth and seventh decade as shown in Fig. 7.

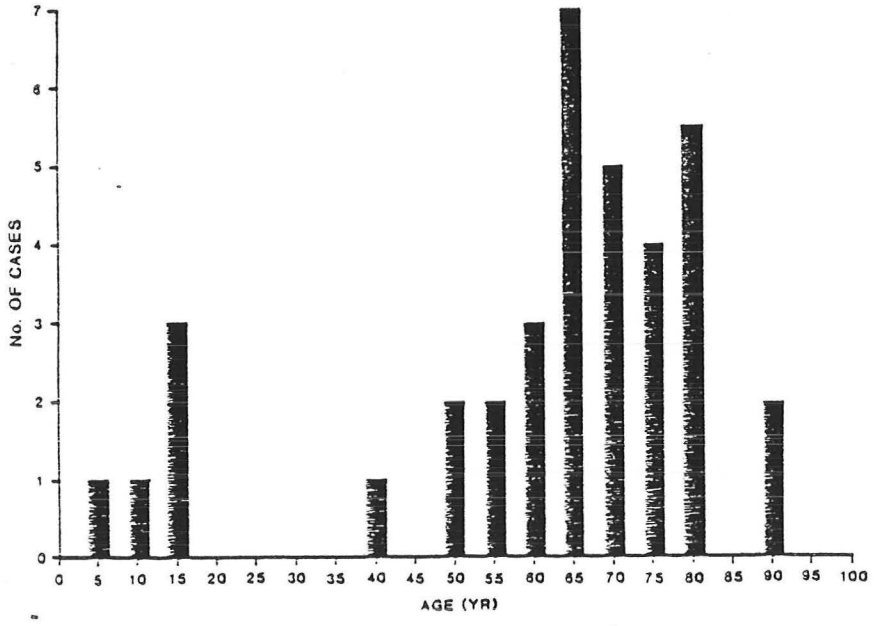

Fig. 7
Age Distribution of 39 cases of primary small intestinal lymphoma (58)

The presenting symptoms in these 39 patients are listed in Table 11.

TABLE 12
PRESENTING SYMPTOMS IN 39 PATIENTS WITH PRIMARY SMALL INTESTINAL LYMPHOMA (58)

Abdominal pain	77%
Signs of obstruction	65%
Diarrhea	28%
Abdominal mass	31%
GI bleeding	3.1%
Malabsorption	2.8%

It should be noted that two-thirds of the patients presented with signs of small bowel obstruction which is a common feature in most series on small intestinal lymphoma of the Western variety. It is of interest that 11 of the 39 patients had villus atrophy, but none had a diagnosis of celiac disease prior to presentation. Ileum is the most common site of the lesion followed by jejunum, while a duodenal lymphoma is uncommon. The macroscopic appearance at exploration is that of polypoid mass or diffuse infiltration of a variable length of the intestine.

Classification

In the older series, classified with Rappaport's system, large cell (histiocytic) lymphoma predominate, comprising 60 to 70 percent of all cases of primary small intestinal lymphoma (4,60). The remaining cases were either lymphocytic or mixed cell lymphomas. In the newer series it has become apparent that most of the small intestinal lymphomas are of follicle center cell origin similar to gastric lymphomas (61). In the series of 39 patients reported above, 75% of the lymphomas stained positive for a monoclonal surface immunoglobulin, indicating a B cell lymphoma despite the fact that only paraffin-embedded tissue was available for study (60). The histologic appearance of the lesion in the small intestine is also very similar to the lesion seen in gastric lymphoma. Typically, there is a very dense plasma cell infiltrate in the lamina propria which displaces but does not invade the mucosal glands. In the deeper layers of the lamina propria the infiltrate consists of a mixture of follicle center cells, small and large cleaved cells and large noncleaved cells, which may be arranged in a follicular or diffuse pattern. These FCCs are the neoplastic cells and invade the glands forming the characteristic lymphoepithelial lesion. In one recent case of primary small intestinal lymphoma where frozen tissue was available for study, it was found that both the invasive FCCs and the noninvasive plasma cells had identical monoclonal surface immunoglobulins (62). This observation strongly suggests a clonal relationship between the FCCs and the plasma cells. Furthermore, the observation reinforces the concept of mucosa-associated lymphoid tissue (MALT). While the events leading to a malignant transformation of the FCCs remain unknown, the FCCs subsequently proliferate and invade the surrounding tissue. Some of the FCCs from the neoplastic clone leave the follicle and are transformed to plasma cells while in passage from the mesenteric lymph nodes to the systemic circulation. The plasma cells from the neoplastic clone eventually home-in in the area of the invasive FCC and then represent the noninvasive differentiated end of the malignant clone.

Thus, the evidence is emerging that small intestinal lymphoma of the Western type is identical to gastric lymphoma in that they are derived from follicle center cells and that they both behave in an identical fashion, i.e., remain localized lesions at their site of origin for a substantial period.

Treatment

The primary treatment of small intestinal lymphoma is surgical resection of the lesion. As in gastric lymphoma, radical resection should be attempted. Obviously, surgery should be followed by chemotherapy in stage III and IV disease. The newer series are too small so far to answer the question whether surgery alone is sufficient in stage IE or whether adjuvant radiotherapy or chemotherapy will provide additional benefit. In stage IIE the surgical resection should be followed by chemotherapy. The newer series contain too few patients treated with multiagent chemotherapy to decide on the optimal treatment modality. Since primary small intestinal lymphoma is such a rare disease, a multicenter prospective study is needed to answer these questions.

Eastern lymphoma

Case 2: A 29-year-old Latin-American male who developed chronic diarrhea while living in Mexico. In the 5 to 6 months prior to his admission to Parkland Memorial Hospital, his diarrhea worsened and changed from watery to bloody diarrhea. The diarrhea was associated with abdominal pain, anorexia, and a weight loss of 40 pounds. On admission he was cachectic, dehydrated and in moderate pain. Abdominal exam was unremarkable, but he was diffusely tender on rectal examination, and the stool was blood streaked. A methylene blue stain of the stool demonstrated sheets of white blood cells. Proctoscopy revealed friable mucosa with scattered punctate ulcers. The amebic titer was 1:128 and treatment with flagyl and iodoquinol was started for presumed amebic colitis. He subsequently underwent colonoscopy which demonstrated focal areas with inflammed mucosa and aphthous ulcers. Initial biopsies from these lesions were interpreted as showing nonspecific inflammation. His treatment was changed to prednisone for presumed Crohn's disease. Further workup included an upper GI with SBFT which demonstrated a large ulcerated mass lesion in the second part of the duodenum. Endoscopic biopsies of the mass showed lymphoma. Reexamination of the colonic biopsies demonstrated that the histologic appearance was identical to the duodenal lesion confirming the diagnosis of lymphoma involving both the small intestine and colon. In addition, serum electrophoresis showed an abnormal band in the α_2 and β region which is compatible with an abnormal IgA (α-chains). This patient is the first case of α-chain disease seen at this institution.

The particular form of lymphoma of the small intestine encountered in many underdeveloped countries has been referred to as Mediterranean lymphoma, Middle Eastern lymphoma or α-chain disease (63-67). The term immunoproliferative small intestinal disease (IPSID) was recommended by WHO in 1976 to

embrace these different terms and to define a clinical condition that may develop into intestinal lymphoma (68). The majority of patients was initially encountered and described in reports from the Middle East and the Mediterranean basin (63-66). A number of patients have now been reported from South and Central Africa, Southeast Asia, as well as South and Central America (69,70). The common denominators to the high prevalance of IPSID in these countries is a low socioeconomic status in most patients with resulting poor nutrition, poor hygiene and a high rate of bacterial and parasitic enteric infections (71,72).

Presentation

The immunoproliferative small intestinal disease may be distinguished from Western lymphoma by the age of presentation, the presenting symptoms and the involved area of the small intestine.

The highest incidence of IPSID is seen in the second and third decade of life as shown in Fig. 8.

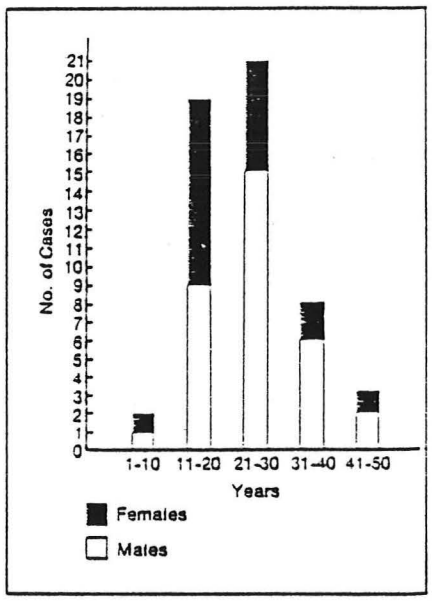

Fig. 8 - Age Incidence of IPSID in 53 Patients (73)

The presenting symptoms are listed in Table 13.

TABLE 13 - CLINICAL PRESENTATION IN 80 PATIENTS WITH IPSID (72)

Chronic diarrhea	95%
Steatorrhea	62%
Abdominal pain	98%
Weight loss	92%
Fever	42%
Vomiting	35%
Abdominal mass	21%

As evident from Table 12, chronic diarrhea is almost invariably present with frank malabsorption in about two-thirds of the patients. Malabsorption may be present in an even higher proportion of patients because tests for malabsorption have not been included in many series from the Mediterranean countries. Malabsorption accounts in part for the prominent weight loss. In about one-third of the patients there is evidence of parasitic infestation.

Barium studies with small bowel follow-through are abnormal in nearly all cases and may show edema of the bowel wall, multiple filling defects, strictures, and dilatation involving long segments of the proximal small intestine and duodenum. The clinical presentation combined with the radiological appearance are almost pathognonomic for IPSID when seen in a third world country. The diagnosis is established by histological examination of tissue obtained at surgery or by small bowel biopsy.

Classification

The pathologic findings on the histological examination of the intestine can be separated into two phases: a prelymphomatous and a lymphomatous phase (71). In the prelymphomatous phase there is a dense infiltrate of plasma cells in the lamina propria which effaces the normal villus pattern. The villus changes are proportional to the degree of cellular proliferation. Eventually, small mucosal ulcerations may be seen. In the lymphomatous phase tumor nodules appear in the mucosa composed of immature plasma cells and lymphocytes. The tumor nodules will eventually invade the entire thickness of the bowel wall.

The term α-chain disease was introduced by Seligman in 1968 when an abnormal IgA immunoglobulin was found in the serum, urine and the proliferating plasma cells in a young Syrian woman with small intestinal lymphoma (74). The abnormal immunoglobulin was found to be an α_1 heavy chain molecule without light chains. In all cases studied so far by Seligman (73), the abnormal IgA has been found to belong to the α_1 subclass. There may be partial or complete deletion of the variable (V_H) and first constant region (C_H1) whereas the carboxyterminal portion of the molecule remains intact (75). α-chain disease thus belongs to the group of heavy chain diseases originally described by Franklin (76). It should be noted that IPSID has also been described with gamma heavy chain disease and with monoclonal IgG-kappa and IgA-kappa with a complete molecule (77,78). Thus, the presence of a clone of

plasma cells synthesizing α_1-chains is not an obligatory requirement for the diagnosis of IPSID. The abnormal protein appears as a broad band in the α_2 and β regions on serum electrophoresis when it is present in sufficient quantities. However, in more than 50% of cases the abnormal protein is not detected by serum electrophoresis, and in these cases more sensitive assays are required utilizing immunoelectrophoresis with specific antibodies against the α_1 heavy chains (75). The abnormal protein may also be detected in jejunal secretions and in the plasma cells in the lamina propria (79). The abnormal protein is found in the serum in 20 to 69% of cases depending on the sensitivity of the assay (72). The presence of the abnormal protein is also dependent on the stage of the disease in that it is often detected in the prelymphomatous phase, while it is rarely present in the lymphomatous phase.

In earlier studies of IPSID the lymphoma was classified as an immunoblastic lymphoma due to the distinct monoclonal plasma cell infiltrate (80). In a recent study the histologic characteristics of Western and Eastern lymphoma were compared and were found to be very similar (62). The histologic characteristics of the two lymphoma types are shown in Table 14.

TABLE 14 - THE HISTOLOGIC APPEARANCE AND IMMUNOCHEMICAL STAINING REACTIONS IN EASTERN AND WESTERN LYMPHOMA (62)

	Eastern	Western
Mucosal plasma cell infiltrate	+	+
Band-like infiltration of FCCs	+	+
Gland invasion by FCCs	+	+
Immunohistochemistry		
Plasma cells	monotypic α,J	monotypic μ, κ
FCCs		
CI_g	-	trace μ, κ
SI_g	ND	μ, κ

The only difference between the two lymphomas is that the plasma cells in the Eastern lymphoma express monoclonal α chains and J chains, whereas the Western lymphoma expresses monoclonal heavy and light chains. The invasive cells in Eastern lymphoma is of FCC origin as in Western lymphoma. It is therefore thought that both types of lymphomas share a common pattern of histogenesis. Since many cases of IPSID are characterized by recurrent bacterial and parasitic gastrointestinal infections prior to the development of the disease, it has been speculated that the prolonged and intense antigenic stimulation of the mucosa-associated lymphoid tissue may result in malignant transformation of a clone of FCCs in a small intestinal lymphoid nodule. The transformed and activated FCCs differentiate into α chain synthesizing plasma cells which home in around the neoplastic FCCs in the small intestine. It remains unexplained why IPSID is associated with α chain synthesizing plasma cells. The abnormal immunoglobulin is, however, ineffectual in antigen neutralization, which may

in part account for the diffuse involvement of the intestine in Eastern lymphoma.

For these reasons, Eastern and Western lymphomas can be classified as FCC lymphoma in this unifying hypothesis and therefore on histologic grounds East meets West.

Treatment

In the prelymphomatous phase of IPSID treatment with tetracycline has been shown to induce complete clinical and histologic remission (71,72). In the lymphomatous phase treatment with radiotherapy and/or chemotherapy is required and successful treatment with multiagent chemotherapy such as CHOP and CVP has been described but only in case reports or small series. The optimal chemotherapy regimen remains to be defined.

Surgical resection has been employed in some series but is now discouraged due to the extent of the disease which requires large resections in patients who are debilitated and malnourished.

It should also be emphasized that intestinal lymphoma in IPSID appears to develop from an apparently benign and potentially curable phase (prelymphomatous phase) and therefore early diagnosis and treatment are important to prevent the development of the terminal phase of the disease. An improvement in the living conditions in these countries may have a major impact on the incidence of IPSID.

Celiac disease and small intestinal lymphoma

The interesting association between celiac disease (nontropical sprue) and the development of small intestinal lymphoma has been recognized for some time (81). A collaborative study was started in England in 1978 with the aim of collecting all cases of documented celiac disease who subsequently developed a malignancy. A total of 400 cases were collected, of which 235 patients fulfilled the acceptance criteria which included a histologic confirmed malignancy (82). In 133 patients the malignant tumor was a lymphoma which was classified as shown in Table 15.

TABLE 15
CLASSIFICATION OF MALIGNANT LYMPHOMA IN 133 PATIENTS WITH CELIAC DISEASE (82).

	No
Well-differentiated Lymphocytic	2
Undifferentiated Large Cell	9
Histiocytic	107
Mycosis Fungoides	1
Unclassified	14
Total	133

The majority of the lymphomas (80%) were classified as histiocytic lymphoma. Most of the lymphomas presented as a small intestinal lesion. Isaacson and Wright have recently presented evidence that the lymphoma in celiac disease is of single histogenetic type which they called malignant histiocytosis (83). The evidence was based on morphologic and immunohistochemical studies on formalin-fixed and later fresh tissue which appeared to confirm the histiocytic properties (monocyte/macrophage derivation) of the malignant cells. The lymphoma would thus appear to be distinct from the FCC derived lymphomas of the small intestine.

The evidence for a histiocytic origin was, however, recently disputed by two reports published a few months apart (84,85). The paper from this country describes a single patient with a 25-year history of celiac disease who developed an intestinal lymphoma. Fresh tissue was obtained at the surgical exploration and suspension of tumor cells were shown to form E-rosettes with sheep erythrocytes. Furthermore, the tumor cells stained positive with two pan-T-cell antibodies (CD2 and CD5) and negative for monoclonal surface immunoglobulins confirming the T cell nature of the tumor cells. The other report describes four patients from England with celiac disease and intestinal lymphoma where fresh tissue also was available for study. The tumor tissues were screened with a panel of 18 monoclonal antibodies. The tumor cells were unreactive with antibodies to B-cell antigens and macrophages but strongly positive with the anti T-cell antibody CD7. Furthermore, DNA hybridisation studies on extracted DNA from the tumor tissue showed rearrangement of the T cell receptor β-chain gene in all four patients.

The two reports confirm that the lymphoma associated with celiac disease is distinct from the common form of intestinal lymphoma which is B cell derived (FCC). The T cell origin of the lymphoma in celiac disease needs to be confirmed in a larger series of patients. The misclassification of the

lymphoma as histiocytic is probably due to the fact that a heavy reactive infiltrate of histiocytes is found in these lymphomas. As mentioned previously, T cells are found normally both within the mucosa and in the lamina propria. A characteristic histologic feature of celiac disease is a heavy T cell infiltrate intraepithelially. It is possible that the lymphoma develops from a neoplastic transformation of a clone of these intraepithelial T cells.

It is noteworthy that eleven patients of a series of 39 patients with primary small intestinal lymphoma presented previously had various degrees of villus atrophy, although none had a diagnosis of celiac disease at the time of presentation. These eleven patients may have had a latent form of celiac disease which will only be manifest on gluten challenge. A recent case report has described the association between latent celiac disease and intestinal lymphoma (86). The patient presented with intestinal lymphoma and had equivocal villus changes in the mucosa not involved by the lymphoma. On gluten challenge she developed partial villus atrophy and frank fat malabsorption. The villus morphology normalized on a gluten-free diet. This interesting case report raises the possibility that a subset of patients with celiac disease has a latent form of the disease with a similar (?) susceptibility for the development of lymphoma.

Immunodeficiency and small intestinal lymphoma

Immunosuppression in transplant patients has been associated with isolated cases of primary small intestinal lymphoma (87). Similarly, a few cases have been described in congenital immunodeficiency syndromes such as X-linked immunodeficiency and Wiskott-Aldrich syndrome (88,89). Nodular lymphoid hyperplasia of lymphoid tissue throughout the intestine is observed in association with immunodeficiency syndromes but has rarely been associated with the development of intestinal lymphoma. Benign nodular lymphoid hyperplasia without demonstrable immunodeficiency but with subsequent development of intestinal lymphoma has recently been described (90,91). Not surprisingly, an increasing number of primary small intestinal lymphomas are now being reported in AIDS patients (92-94). A characteristic feature of AIDS is chronic enteric infections with a number of pathogens similar to patients who develop Eastern lymphoma. The intense antigenic stimulation of the mucosa-associated lymphoid tissue may ultimately result in malignant transformation of a clone of FCCs and development of lymphoma.

Colonic lymphoma

As indicated in Table 1 colonic lymphoma is the rarest type of primary gastrointestinal lymphomas. A suspected colonic malignancy is much more likely to be adenocarcinoma. In large series colonic lymphoma accounts only for 0.2 to 0.6 percent of colonic malignancies (95,96). The most frequent location of a colonic lymphoma is the cecum followed by the rectum and the remainder of the colon. The age-related incidence is similar to gastric and small intestinal lymphoma (Western type) with most cases presenting in the sixth and seventh decade (96).

Presentation

The presenting symptoms in a series of patients with colonic lymphoma seen at the Mayo Clinic are listed in Table 16 (97).

TABLE 16 - PRESENTING SYMPTOMS IN 44 PATIENTS WITH COLONIC LYMPHOMA

Abdominal pain	90%
Weight loss	80%
Change in bowel habits	76%
Rectal bleeding	26%
Anorexia	28%

Rectal bleeding, diarrhea and tenesmus were the most common symptoms in rectal lymphoma (98). The symptoms are thus very similar to those seen in patients with colon cancer, and the two conditions cannot be distinguished on clinical grounds. The barium enema is abnormal in most patients and may demonstrate a polypoid lesion, an ulcerated mass or an infiltrated stricture. The radiologic appearance is again similar to the findings in colonic carcinoma. In rare instances colonic lymphoma may present as diffuse lymphomatous colitis which on barium enema or colonoscopy is indistinguishable from ulcerative colitis or Crohn's disease (99,100). Case 2 in this protocol presents this interesting feature. The diagnosis is established from histologic examination of tissue obtained at colonoscopy or at surgical exploration.

Classification

The colonic lymphomas are invariably of FCC derivation (centrocytic and/or centroblastic) or large cell (histiocytic) with the Rapporport classification. In the few studies where frozen tissue was available for immunohistochemistry monoclonal surface immunoglobulins were found on the neoplastic cells documenting a B cell origin (44). The histologic appearance of the lymphoma is similar to gastric and small intestinal lymphoma as described in the previous sections.

Treatment

Radical surgical resection should be attempted as in other primary gastrointestinal lymphoma. Patients who have had a radical resection have a better prognosis than those who only received a palliative resection (96). The feasability of radical resection is in part a reflection of the stage of the disease. The role of surgery in stage III and IV is debated, but debulking may be of importance in reducing the tumor mass and reducing the risk of postoperative complications (perforation, bleeding) when radiotherapy and chemotherapy are employed. The precise role of radiotherapy and chemotherapy in stage IE and IIE is still undefined. Chemotherapy is indicated in stage III and IV. The value of adjuvant chemotherapy in colonic lymphoma cannot be assessed from the current literature.

Summary and Conclusions

In summary, the majority of primary gastrointestinal lymphomas appear to be B cell lymphomas derived from a common ancestor, the follicle center cell. It is expected that the current complex classification systems may be replaced by a simplified system with the use of modern histologic techniques that include a battery of monoclonal cell markers. The former distinction between Western and Eastern lymphoma is no longer tenable, and the only difference between the two types is the more extensive involvement of the small intestine in the Eastern lymphoma. In addition, true histiocytic lymphoma of the gastrointestinal tract is exceedingly rare. The lymphoma associated with celiac disease previously classified as malignant histiocytosis now appears to be a T cell lymphoma. The therapeutic approach to gastrointestinal lymphoma is currently being defined. Radical surgery may be sufficient as the sole treatment modality in stage IE disease, and radical surgery followed by combination chemotherapy has demonstrated promising results in stage IIE, III and IV.

REFERENCES

1. Hodgkin T. On some morbid appearances of the absorbent glands and spleen. Med Chir Trans 17:68, 1832.

2. Billroth T. Multiple lymphome. Erfolgreiche Behandlung mit Arsenik. Wien Med Wochenschr 21:1066, 1871.

3. Dawson IMP, Cornes JS, Morson BC. Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. Br J Surg 49:80, 1961.

4. Skinner JM. Gastrointestinal lymphoma. Pathology 17:193, 1985.

5. Parrott, DMV. The gut as a lymphoid organ. Central or peripheral lymphoid tissue? Clinics in Gastroent 5:211, 1976.

6. Pollard M, Sharon N. Responses of Peyer's patches in germ-free mice to antigenic stimulation. Infect Immunol 2:96, 1970.

7. Ferguson A, Parrott DMV. The effect on antigen deprivation on thymus dependent and thymus independent lymphocytes in the small intestine of the mouse. Clin Exp Immunol 12:477, 1972.

8. Wolf JL, Rubin DH, Finberg R, et al. Intestinal M cells: a pathway for entry of reovirus into the host. Science 212:471, 1981.

9. Targan SR, Kagnoff MF, Brogan MD, Shanahan F. Immunologic mechanisms in intestinal diseases. Ann Intern Med 106:853, 1987.

10. Guy-Grand D, Griscelli C, Vassalli P. The gut associated lymphoid system: nature and properties of the large dividing cells. Eur J Immunol 4:435, 1974.

11. Cerf-Bensussan N, Schneeberger EE, Bhan AK. Immunohistologic and immunoelectron microscopic characterization of the mucosal lymphocytes of human small intestine by the use of monoclonal antibodies. J Immunol 130:2615, 1983.

12. Shanahan F, Brogan M, et al. Spontaneous and lymphokine activated killer cells exist in the human intestine. Gastroenterology 90:1629, 1986.

13. Carman PS, Ernst PB, et al. Intraepithelial leucocytes contain a unique subpopulation of NK-like cytotoxic cells active in the defence of gut epithelium to enteric murine corona virus. J Immunol 136:1548, 1986.

14. Kuhn LC, Kraehenbuhl J-P. The sacrificial receptor-translocation of polymeric IgA across epithelia. Trends in Biochem Sciences 7:299, 1982.

15. Isaacson PG, Spencer J. Malignant lymphoma of mucosa-associated lymphoid tissue. Histopathology 11:445, 1987.

16. Green JA, Dawson AA, Jones PF, Brunt PW. The presentation of gastrointestinal lymphoma: study of a population. Br J Surg 66:798, 1979.

17. Back Hans, Gustavsson B, Ridell B, Rodjer S, Westin J. Primary gastrointestinal lymphoma. Incidence, clinical presentation, and surgical approach. J Surg Oncol 33:234, 1986.

18. Saraga P, Hurliman J, et al. Lymphoma and pseudolymphoma of the gastrointestinal tract. Human Pathol 12:713, 1981.

19. Weingrad DN, Decosse JJ, Sherlock P, Straus D, Lieberman PH, Filippa DA. Primary gastrointestinal lymphoma: A 30-year review. Cancer 49:1258, 1982.

20. Filippa DA, Lieberman PH, Weingrad DN, Decosse JJ, Bretsky SS. Primary lymphomas of the gastrointestinal tract. Analysis of prognostic factors with emphasis on histological type. Am J Surg Pathol 7:363, 1983.

21. Isaacson P, Wright DH, Judd MA, Mepham BL. Primary gastrointestinal lymphomas. A classification of 66 cases. Cancer 43:1805, 1979.

22. Contreary K, Nance FC, Becker WF. Primary lymphoma of the gastrointestinal tract. Ann Surg 5:593, 1980.

23. Rosenfelt F, Rosenberg SA. Diffuse histiocytic lymphoma with gastrointestinal tract lesions. The Stanford experience. Cancer 45:2188, 1980.

24. Lewin KJ, Ranchod M, Dorfman RF. Lymphomas of the gastrointestinal tract. A study of 117 cases presenting with gastrointestinal disease. Cancer 42:693, 1978.

25. Aozasa A, Tsujimoto M, Inoue A, Nakagawa K., Hanai J, Kurata A, Nosaka J. Primary gastrointestinal lymphoma. A clinicopathologic study of 102 patients. Oncology 42:97, 1985.

26. Dragosics B, Bauer P, Radaszkiewicz T. Primary gastrointestinal non-Hodgkin's lymphomas. A retrospective clinicopathologic study of 150 cases. Cancer 55:1060, 1985.

27. Papadimitriou CS, Papacharalampous NX, Kittas C. Primary gastrointestinal malignant lymphomas. A morphologic and immunohistochemical study. Cancer 55:870, 1985.

28. Al-Bahrani ZR, Al-Mondhiry H, Al-Saleem T. Clinical and pathologic subtypes of primary intestinal lymphoma. Cancer 52:1666, 1983.

29. Blackledge G, Bush H, Dodge OG, Crowther D. A study of gastrointestinal lymphoma. Clin Oncol 5:209, 1979.

30. Carbone PP, Kaplan HS, et al. Report of the committee on Hodgkin's disease staging classification. Cancer Res 31:1860, 1971.

31. Musshoff K, Schmidt-Vollmer H. Prognosis of non-Hodgkin's lymphoma with special emphasis on the staging classification. Z. Krebsforsch 83:323, 1975.

32. Come SE, Chabner BA. Staging in non-Hodgkin's lymphoma: Approach, results and relationship to histopathology. Clinics in Haematology 8:645, 1979.

33. Lee JR, Gray SW, Brown BC, Skandalakis JE. Diffuse histiocytic lymphomas of the gastrointestinal tract in the adult. Surgery Gynecol Obstet 157:286, 1983.

34. Rappaport H. Tumors of the hematopoietic system. National Research Council, Washington, D.C. Committee on Pathology. Atlas of Tumor Pathology, Section III, Fasc 8, 1966.

35. Morris MW, Davey FR. Immunologic and cytochemical properties of histiocytic and mixed histiocytic-lymphocytic lymphomas. Am J Clin Pathol 63:403, 1975.

36. Lukes RJ, Collins RD. A functional approach to the classification of malignant lymphoma. Recent results. Cancer Res 46:18, 1974.

37. Lenner K, Mohri N, et al. The histopathology of malignant lymphoma. Br J Haematol, Suppl II 31:193, 1975.

38. National Cancer Institute sponsored study of classification of non-Hodgkin's lymphomas. Cancer 49:2112, 1982.

39. Shiu MH, Nisce LZ, Pinna A, Straus DJ, Tome M, Filippa DA, Lee BJ. Recent results of multimodal therapy of gastric lymphoma. Cancer 58:1389, 1986.

40. Lecomte D, Parlier Y, Gorin NC, Najman A. Prognostic failure of new working formulation in gastrointestinal non-Hodgkin's lymphomas. Lancet ii:1465, 1982.

41. Brooks JJ, Enterline HT. Primary gastric lymphomas. A clinicopathologic study of 58 cases with long-term follow-up and literature review. Cancer 51:701, 1983.

42. Isaacson PG, Spencer J, Finn T. Primary B-cell gastric lymphoma. Hum Pathol 17:72, 1986.

43. Moore I, Wright DH. Primary gastric lymphoma - a tumour of mucosa-associated lymphoid tissue. A histological and immunohistochemical study of 36 cases. Histopathology 8:1025, 1984.

44. Grody WW, Weiss LM, Warnke RA, Magidson JG, Hu E, Lewin KJ. Gastrointestinal lymphomas. Immunohistochemical studies on the cell of origin. Am J Surg Pathol 9:328, 1985.

45. Jacobs DS. Primary gastric malignant lymphoma and pseudolymphoma. Am J Clin Pathol 40:379, 1969.

46. Smith J, Helwig E. Malignant lymphoma of the stomach. Am J Pathol 34:553, 1958.

47. Lerman-Sagie T, Ziv Y, Rubin M, More C, Dintsman M. Gastric lymphoma versus pseudolymphoma: The importance of immunological differentiation. Am J Gastroent 80:763, 1985.

48. Tokunaga O, Watanabe T, Morimatsu M. Pseudolymphoma of the stomach. A clinicopathologic study of 15 cases. Cancer 59:1320, 1987.

49. Seo IS, Binkley WB, Warner TFCS, Warfel KA. A combined morphologic and immunologic approach to the diagnosis of gastrointestinal lymphomas. Malignant lymphoma of the stomach (A clinicopathologic study of 22 cases). Cancer 49:493, 1982.

50. Shiu MH, Karas M, Nische L, Lee BJ, Filippa DA, Lieberman PH. Management of primary gastric lymphoma. Ann Surg 195:196, 1982.

51. Dworkin B, Lightdale CJ, Weingrad DN, Decosse JJ, Lieberman P, Filippa DA, Sherlock P, Straus D. Primary gastric lymphoma. A review of 50 cases. Dig Dis Sci 27:986, 1982.

52. Maor MH., Maddux B, Osborne BM, Fuller LM, Sullivan JA, Nelson RS, Martin RG, Libshitz HI, Velasquez WS, Bennett RW. Stages IE and IIE non-Hodgkin's lymphomas of the stomach. Comparison of treatment modalities. Cancer 54:2330, 1984.

53. Barzilay J, Rakowsky E. Gastric lymphoma: A clinical study of 28 cases and an evaluation of prognostic factors. Clin Oncol 10:233, 1984.

54. Shimm DS, Dosoretz DE, Anderson T, Linggood RM, Harris NL, Wang CC. Primary Gastric lymphoma. An analysis with emphasis on prognostic factors and radiation therapy. Cancer 52:2044, 1983.

55. Paulson S, Sheehan RG, Stone MJ, Frenkel EP. Large cell lymphomas of the stomach: Improved prognosis with complete resection of all intrinsic gastrointestinal disease. J Clin Oncol 1:263, 1983.

56. Sheridan WP, Medley G, Brodie GN. Non-Hodgkin's lymphoma of the stomach: A prospective pilot study of surgery plus chemotherapy in early and advanced disease. J Clin Oncol 3:495, 1985.

57. Randall J, Obeid ML, Blackledge GRP. Haemorrhage and perforation of gastrointestinal neoplasms during chemotherapy. Ann R Coll Surg Engl 68:286, 1986.

58. Steward WP, Harris M, Wagstaff J, Scarffe JH, Deakin DP, Todd DH, Crowther D. A prospective study of the treatment of high-grade histology non-Hodgkin's lymphoma involving the gastrointestinal tract. Am J Cancer Oncol 21:1195, 1985.

59. Cooper BT, Read AE. Small intestinal lymphoma. World J Surg 9:930, 1985.

60. Morgan DR, Holgate CS, Dixon MF, Bird CC. Primary small intestinal lymphoma: A study of 39 cases. J Pathol 147:211, 1985.

61. Isaacson P, Al-Dewachi H, Mason D. Middle Eastern Intestinal lymphoma: a morphological and immunohistochemical study. J Clin Pathol 36:489, 1983.

62. Isaacson P, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive type of B-cell lymphoma. Cancer 52:1410, 1983.

63. Nassar VH, Salem PA, Shahid MJ, et al. "Mediterranean abdominal lymphoma" or immunoproliferative small intestinal disease. Part II: Pathological aspects. Cancer 41:1340, 1978.

64. Asselah F, Slavin G, Sowter G, Asselah H. Immunoproliferative small intestinal disease in Algerians. I. Light microscopic and immunochemical studies. Cancer 52:227, 1983.

65. Omar YT, Al-Nakib B, Jacob GS, Ali SM, Temmim L, Radhakrishnan S, Fayaz MS. Primary gastrointestinal lymphoma in Kuwait. An 11-year retrospective analysis of 108 cases. Eur J Cancer Clin Oncol 21:573, 1985.

66. Al-Bahrani Z, Al-Mondhiry H, Al-Saleem T, Zaini S. Primary intestinal lymphoma in Iraqi children. Oncology 43:243, 1986.

67. Al-Mondhiry H. Primary lymphomas of the small intestine: East-West contrast. Am J Hematol 22:89, 1986.

68. Alpha-chain disease and related small intestinal lymphoma. A memorandum. Bull. WHO 54:615, 1976.

69. Novis BH. Primary intestinal lymphoma in South Africa Isr J Med Sci 15:386, 1979.

70. Gray GM, Rosenberg SA, Cooper AD, Gregory PB, Stein DT, Herzenberg H. Lymphomas involving the gastrointestinal tract. Gastroenterology 82:143, 1982.

71. Khojasteh A, Haghshenass M, Haghighi P. Immunoproliferative small intestinal disease. N Engl J Med 308:1401, 1983.

72. Rambaud J-C. Small intestinal lymphomas and alpha-chain disease. Clin in Gastroent 12:743, 1983.

73. Seligmann M. Immunochemical, clinical, and pathological features of α-chain disease. Arch Intern Med 135:78, 1975.

74. Seligmann, M, Danon F, Hurez D, Mihaesco E, Preud'Homme J-L. Alpha-chain disease: A new immunoglobulin abnormality. Science 162:1396, 1968.

75. Seligmann M, Mihaesco E, Preud'Homme J-L, Danon F, Brouet J-C. Heavy chain diseases: Current findings and concepts. Immunological Rev 48:145,1979.

76. Franklin EC, Lowenstein B, et al. Heavy chain disease - a new disorder of serum gammaglobulins: report of the first case. Am J Med 37:332, 1964.

77. Ramos L, Marcos J, et al. Radiological characteristics of primary intestinal lymphoma of the "Mediterranean" type. Radiology 126:379, 1978.

78. Cabrera A, de la Pava S, et al. Intestinal localization of Waldenstrom's disease. Arch Intern Med 114:399, 1964.

79. Rambaud J-C, Galian A, Danon FG., et al. Alpha-chain disease without qualitative serum IgA abnormality. Report of two cases, including a "nonsecretory" form. Cancer 51:686, 1983.

80. Rappaport H, Ramot, B, Hulu N, Park JK. The pathology of so-called Mediterranean abdominal lymphoma with malabsorption. Cancer 29:1502, 1972.

81. Holmes GKT, Stokes PL, et al. Coeliac disease, gluten-free diet and malignancy. Gut 17:612, 1976.

82. Swinson CM, Slavin G, et al. Coeliac disease and malignancy. Lancet i:111, 1983.

83. Isaacson PG, Wright DH. Malignant histiocytosis of the intestine: its relationship to malabsorption and ulcerative jejunitis. Hum Pathol 9:661, 1978.

84. Loughran, Jr. TP, Kadin ME, Deeg HJ. T-cell intestinal lymphoma associated with celiac sprue. Ann Intern Med 104:44-1986.

85. Isaacson PG, Spencer J, et al. Malignant histiocytosis of the intestine: A T-cell lymphoma. Lancet ii:688, 1985.

86. Freeman HJ, Chiu BK. Multifocal small bowel lymphoma and latent celiac sprue. Gastroenterology 90:1992, 1986.

87. McFamaney JP, Neifeld JP, et al. Primary gastric lymphoma following renal transplantation. J Surg Oncol 18:265, 1981.

88. Rosen FS. Primary immunodeficiency. Ped Clin North Am 21:533, 1974.

89. Faraci, RP, Hoffstrand HJ, et al. Malignant lymphoma of the jejunum in a patient with Wiskott-Aldrich syndrome. Arch Surg 110:569, 1975.

90. Rambaud, J-C, de Saint-Louvent P, Marti R, Galian A, Mason DY, Wassef M, Licht H, Valleur P, Bernier J-J. Diffuse follicular lymphoid hyperplasia of the small intestine without primary immunoglobulin deficiency.

91. Matuchansky C, Touchard G, Lemaire M, Babin P, Demeocz F, Fonck Y, Meyer M, Preud'Homme, J-L. Malignant lymphoma of the small bowel associated with diffuse nodular lymphoid hyperplasia.

92. Steinberg JJ, Bridges N, Feiner HD, Valensi Q. Small intestinal lymphoma in three patients with acquired immune deficiency syndrome. Am J Gastroent 80:21, 1985.

93. Collier PE. Small bowel lymphoma associated with AIDS. J Surg Oncol 32:131, 1986.

94. Cappell MS, Chow J. HTLV-I associated lymphoma involving the entire alimentary tract and presenting with an acquired immune deficiency. Am J Med 82:649, 1987.

95. Jinnai D, Iwasa Z, et al. Malignant lymphoma of the large intestine. Jap J Surg 13:331, 1983.

96. Richards MA. Lymphoma of the colon and rectum. Postgrad Med j 62:615, 1986.

97. Wychulis AR, Beahrs OH, Woolner LB. Malignant lymphoma of the colon. Arch Surg 93:215, 1966.

98. Devine RM, Beart RW, Wolff BG. Malignant lymphoma of the rectum. Dis Colon Rectum 29:821, 1986.

99. Gedgaudas-McClees, RK, Maglinte DDT. Aphthous lesions in nodular lymphoma of the colon. South Med J 79:907, 1986.

100. Sagar S, Selby P, Sloane J, McElwain TJ. Colorectal lymphoma simulating inflammatory colitis and diagnosed by immunohistochemistry. Postgrad Med j 62:51, 1986.