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Histological and Immunohistochemical Studies on Primary Gastrointestinal Lymphomas

Jung-Dal Lee*, M.D., Young-Hyeh Ko*, M.D., Jeong-Hee Park*, M.D.,
Kyung-Rang Min**, M.D., Kyung-Nam Park**, M.D.

Department of Pathology, Internal Medicine***,
College of Medicine, Hanyang University, Seoul, Korea

To study the characteristics and histogenesis of the malignant lymphomas derived from the gastrointestinal mucosa, histologic and immunohistochemical analyses were performed on a series of 28 malignant lymphomas of the gastrointestinal tract.

By cytomorphologic classification, there were two small lymphocytic lymphomas, one small cleaved cell lymphoma, two mixed small cleaved and large cell lymphomas, 17 large cell lymphomas, one small noncleaved cell lymphoma, three immunoblastic lymphomas, and two lymphoblastic lymphomas. This distribution of histologic types was compatible with that of nodal lymphoma. The lymphomas with poor prognostic histology (23 cases) outnumbered those with favorable prognosis (five cases). Three of 28 cases (one in the stomach and two in the small intestine) had cytologic features consistent with centrocytoid cell lymphoma of the mucosa associated lymphoid tissue and were large cell lymphomas.

Immunophenotypically, 23 cases expressed B-cell markers (82.1%) and three cases reacted with T-cell markers. Two cases did not react with either T-cell or B-cell markers. True histiocytic lymphomas were not identified.

Gastric lymphomas (nine cases) and colorectal lymphomas (three cases) were of B-lymphocyte origin whereas T-cell lymphomas were noted in the small intestine (two cases) and ileocecal region (one case). Three cases of centrocytoid lymphoma were of B-lymphocyte origin.

Histologically B-cell lineage lymphomas were evenly distributed on various histologic subtypes but all T-lineage lymphomas belonged to the large cell type. The two cases with undetermined phenotype were lymphoblastic lymphomas histologically.

This study showed that the primary GIT lymphomas, mostly of B-cell lineage, were not cytomorphologically distinctive from the nodal lymphomas. We feel that centrocytoid cell lymphomas should not be classified as a separate entity among the primary GIT lymphomas.

Key Words: *Malignant lymphomas, G-I tract, Histological Study ; Immunohistochemical Study*

INTRODUCTION

Primary gastrointestinal lymphoma is a very distinct neoplasm differing from node-based malignant lymphomas in both clinical and histogenetic aspects.

Addressfor correspondence: *Jung-Dal Lee, M.D., Department of Pathology Hanyang University Hospital Haengdang-Dong, Sungdong-Ku, 133-792, Seoul, Korea.*

Although the incidence of malignant lymphomas arising in the gastrointestinal tract (GIT) is lower than that of primary adenocarcinoma (1-7% of all malignancies in the stomach, 20% in the small intestine, 0.4% in the large intestine) (Dragosics et al., 1985; Fleming et al., 1982; Freeman et al., 1972), it is the most common extranodal lymphoma (A1-Bahrani et al., 1983; Contreary et al., 1980). Reportedly, the prognosis of primary gastrointestinal lymphomas is better than those of primary adenocarcinoma and node-based malignant lymphomas (Brooks and Enterline, 1983; Contreary et al., 1980; Maor et al., 1984; Weingrad et al., 1982). The favorable survival of gastrointestinal lymphomas may be explained by certain characteristics of GIT lymphomas such as the long period of localization to the GIT wall and late metastases to regional lymph nodes or other organs (Filippa et al., 1983; Moore and Wright, 1984; Weingrad et al., 1982). Recently, efforts have been made to correlate biologic characteristics with the histogenesis of these lymphomas (Isaacson and Wright, 1983; Isaacson et al., 1987; Moor and Wright, 1984; Myhre and Isaacson, 1987). Histologic classification of GIT lymphomas is often difficult because objective criteria as yet have not been formulated (Grody et al., 1985; Weingrad et al., 1982). Moreover, the morphology seen in GIT lymphomas does not fit into the accepted classification and formulation of non-Hodgkin's lymphoma (NHL) which was developed for node-based NHL (Isaacson et al., 1979; Weingrad et al., 1982).
Accordingly, some investigators have compared the origin of gastrointestinal lymphoma with the mucosa associated lymphoid tissue (MALT) of the gastric mucosa and have attempted to clarify the biologic characteristics on the basis of the lineage of neoplastic cells (Isaacson et al., 1987; Myhre and Isaacson, 1987). With the recent advent of monoclonal antibodies reactive in formalin-fixed, paraffin embedded sections as well as in fresh frozen sections, there have been significant advances in the clarification of the cell lineage of neoplasms (Falini and Taylor, 1983; Taylor, 1978). Monoclonal antibodies have made it possible to discriminate between B-,T-lymphocytes, and histiocytes, and to determine the developmental stage of its ontogeny as well as their immunologic characteristics (Grody et al., 1985; Moore and Wright, 1984; Lewin et al., 1978). Although recent studies have used these immunohistochemical techniques to investigate gastrointestinal lymphomas, contradictory results have led to much controversy over the origin of GIT lymphomas. Some authors have insisted that most gastrointestinal lymphomas of B-lineage are characterized by centrocyte-like cells derived from MALT with a favorable prognosis (Isaacson and Wright, 1983; Myhre and Isaacson, 1987). In contrast, however, other authors have demonstrated no significant prognostic and histological difference between GIT lymphomas and node-based NHL, mitigating against the concept of mucosa associated lymphoma (Grody et al., 1985; van Krieken et al., 1982).
In our study, we have examined the histopathologic features of 28 cases of resected gastrointestinal lymphomas and further examined their immunohistochemical characteristics in an attempt to clarify the origin of the neoplastic cells.

MATERIALS AND METHODS

Materials

A total 38 cases of primary gastrointestinal malignant lymphomas were diagnosed during the period from January 1986 through June 1990 (four years and six months). Of these, ten cases were excluded for which only endoscopic biopsy was available. The remaining 28 resected cases were selected for this study. Patient ages ranged from 10 to 81 years (mean, 48 years) with a male to female ratio of 21:7. The location of the tumor included the stomach in 9 cases, small intestine in 10 cases, ileocecal region in 5 cases, and rectosigmoid in 3 cases. One case showed multifocal involvement along the gastrointestinal tract.

All tissues were fixed in 10% neutral formalin after complete gross examination (Ming, 1973). Tissue sections were obtained from the tumor, surrounding mucosa and regional lymph nodes with subsequent histologic processing (Park and Lee, 1991). When necessary, special stains including Gomori's reticulin, periodic acid-Schiff and methyl-green-pyronin were performed. In cases submitted in a fresh state, touch imprints were stained with Romanowsky, periodic acid-Schiff, and Papanicolaou stain.

Methods

Histologic examination

The cases were classified according to the Working Formulation for clinical usage of the National Cancer Institute (NCI sponsored study, 1982). When interpretation was difficult using histology alone, cytology was assessed on touch imprints. Also examined were the histologic changes diagnostic of malignant lymphoma arising in MALT as proposed by Isaacson et al (Isaacson et al., 1987).

Immunohistochemical stains

Immunohistochemical staining was performed using the biotin-streptavidin (B-SA) method (Stravigen, Biogenex Laboratories, San Ramon, Ca, USA). The incubation time for primary antibodies was one hour at room temperature and 30 minutes for the link antibody. After rinsing, the slides were incubated with horseradish peroxidase-conjugated streptavidin. The slides were then counterstained with Meyer's hematoxylin.

The antibodies employed and their specificity are listed in Table 1. Identification was made using MB 2 and L 26 for B-lymphocytes, MT1 and UCHL 1 for T-lymphocytes, and CD 68 for histiocytes.

Interpretation

Sections of normal lymph node and tonsil were used as positive controls for all antibodies. Antibodies were reactive with benign reactive cells as well as with neoplastic cells. Only the neoplastic cells were evaluated once identified on the hematoxylin-eosin stained slide. In general, T-lineage lymphomas contained a few reactive B-lymphocytes, whereas B-lineage lymphomas contained many reactive T-lymphocytes within the tumor or in the surrounding tissue (Figure 1). Neoplastic cells that did not react with any of the antibodies or which gave equivocal staining results were considered as undetermined phenotype.

RESULTS

Cytologic types

Cytologic classification using the Working Formulation (NCI sponsored study, 1982) was performed on well fixed and properly stained slides. Among the 28 cases, 5 cases were low grade non-Hodgkin's lymphoma including small lymphocytic type in 2 cases, small cleaved cell type in 1 case and mixed small cleaved and large cell type in 2 cases. The remaining 23 cases (82.1%) were interpreted as intermediate or high grade. The most common cytologic type was the diffuse large cell (17 cases). Interpretations were made of small non-cleaved cell type (Burkitt's lymphoma) in 1 case, immunoblastic type in 3 cases and lymphoblastic type in 2 cases. Seven of 9 cases of gastric lymphomas, all ten cases of small intestinal lymphomas and all five cases of ileocecal lymphomas were diagnosed as intermediate or high grade lymphomas.

One gastric lymphoma and two small intestinal lymphomas had cytologic features of the centrocytoid cell lymphomas arising from MALT which were also classified as large cell type of NHL. One of these showed features of centrocytoid lymphoma in the lamina propria, but with invasion into the submucosa, had transformed to large cell type (Table 2).

Immunohistochemistry

Immunophenotypic study revealed B-lineage lymphoma in 23 cases (82.1%), T-cell lineage lymphoma in 3 cases (10.7%) and an undetermined phenotype in 2 cases (7.1%). No cases had neoplastic cells reactive for the histiocytic marker (CD68). All gastric lymphomas (nine cases) were of B-lymphocyte origin, whereas the 10 small intestinal lymphomas were classified as B-lineage in 6 cases, T-lineage in 2 cases and undetermined in 2 cases. Of the five cases of ileocecal lymphoma, 4 were of

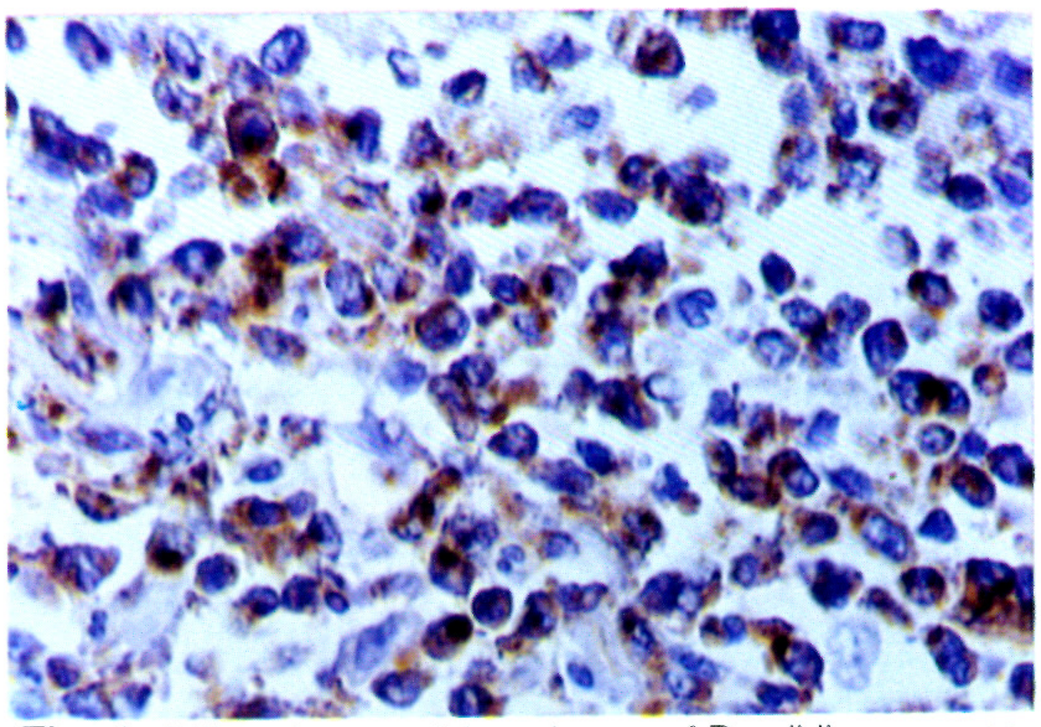

Fig. 1. Diffuse large cell lymphoma of B-cell lineage contains many T-lymphocytes reactive for MT1, Pan-T lymphocyte antibody.

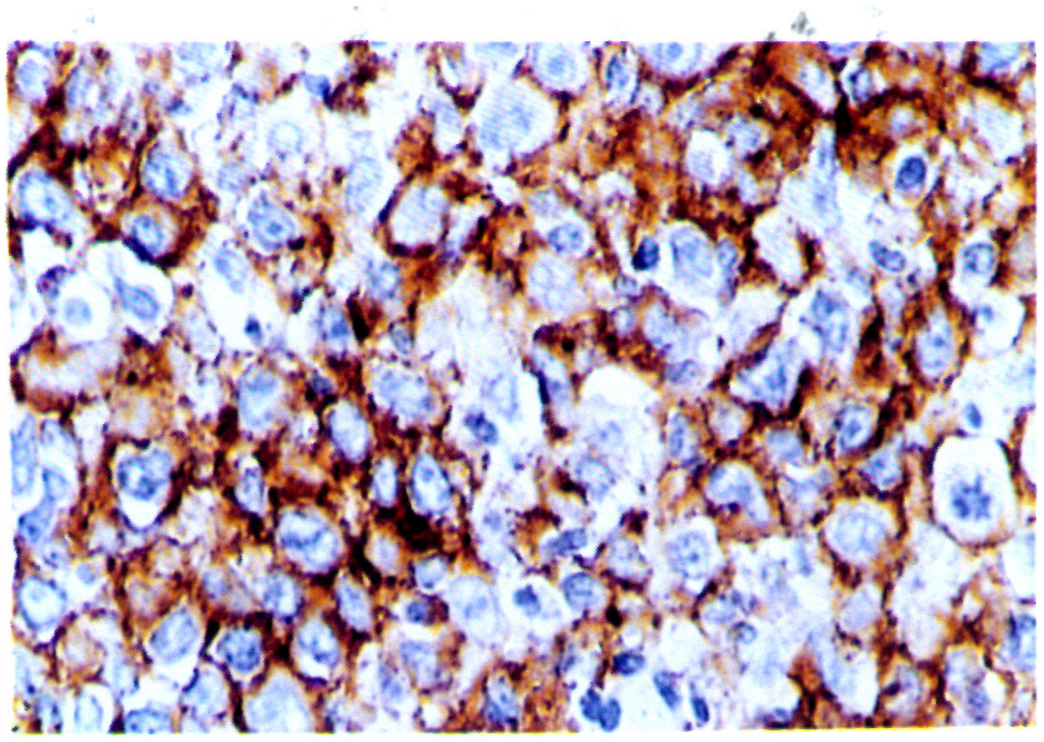

Fig. 2. Diffuse large cell lymphoma of T-cell lineage consists of large pleomorphic cells with bizzare nuclei.

Table 1. Antibodies used in Immunostaining of Gastrointestinal Lymphomas

Antibodies	Source	Specificity
MB 2	Eurodiagnostics, Holland	pan B-cell
CD 20(L26)	DAKO, CA, USA	pan B-cell
MT 1	Eurodiagnostics, Holland	pan T-cell
CD 45Ro (UCHL 1)	DAKO, CA, USA	pan T-cell
CD 68	DADO, CA, USA	Macrophage-Histiocyte

Table 2. Histologic Types of Gastrointestinal Lymphomas

Working Formulation (NCI)	Stomach	Small intestine	Ileocecal	Colon/ Rectum	Multiple	Total
Small lymphocytic	2					2
Small cleaved				1		1
Small & large		2				2
Large	7(1)	5(2)	2	2	1	17
Small non-cleaved			1			1
Immunoblast		1	2			3
Lymphoblast		2				2
Total	9(1)	10(2)	5	3	1	28

Numbers in parenthesis indicate cases with features of malignant lymphoma arising in mucosa-associated lymphoid tissue.

Table 3. Immunologic Types of Gastrointestinal Lymphomas

Markers	Stomach	Small intestine	Ileocecal	Colon/ Rectum	Multiple sites	Total
B-cell	9(1)	6(2)	4	3	1	23(3)
T-cell		2	1			3
Histiocyte						0
Unclassified		2				2
Total	9(1)	10(2)	5	3	1	28(3)

Numbers in parenthesis indicate cases with features of malignant lymphoma arising in mucosa-associated lymphoid tissue.

Table 4. Cytologic and Immunologic Correlation of Gastrointestinal Lymphomas

Working Formulation	B-cell	T-cell	Histiocytic	Unclassified	Total
Small lymphocytic	2				2
Small cleaved	1				1
Small & large	2				2
Small non-cleaved	1				1
Large	14	3			17
Immunoblastic	3				3
Lymphoblastic				2	2
Total	23	3	0	2	28

B-lineage and 1 of T-lineage.

All three cases of T-cell lineage lymphoma occurred in the small intestine or ileocecal region (Table 3).

In respect to analysis of immunophenotype as related to cytologic types, fourteen of 23 B-cell lineage lymphomas were of the large cell type and the remainder were evenly distributed amongst the other histologic types. The three cases of T-lineage lymphoma were of the large cell type (Figure 2). One small cleaved cell type and 3 immunoblastic types were of B-cell lineage (Table 4).

All three cases of centrocytoid lymphomas reacted with pan-B cell markers. The two lymphoblastic types did not react with either pan-B or pan-T antibodies.

DISCUSSION

Primary gastrointestinal lymphomas have been classified with current classification systems developed primarily for nodal lymphomas. A proper classification system for GIT lymphomas has not as yet been established. The Working Formulation for clinical usage (NCI sponsored study, 1982) has been more commonly used than other classification systems including Rappaport (1966), Lukes and Collins (1977), and Kiel (Lennert, 1978).

Recently, Isaacson and Wright (1983) have insisted that gastrointestinal lymphomas could not be adequately classified by the current classification systems and have proposed the new concept of centrocyte-like cell lymphoma derived from mucosa-associated lymphoid tissue. In contrast, other investigators have had no difficulty in applying the current classification system to gastrointestinal lymphomas (Berge et al., 1987; Otto et al., 1981).

Weingrad et al (1982) reported that five percent of gastrointestinal lymphomas could not be classified with the Rappaport classification, 22% with the Lukes and Collins classification, and 26% with the Kiel classification. In our study, none of the cases were difficult to classify.

The distribution of histologic subtypes in gastrointestinal lymphomas has been reported to be markedly different from those of nodal lymphomas (Grody et al., 1985; MacLennan et al., 1981). In the gastrointestinal tract, Hodgkin's disease is very rare while plasmacytoid small lymphocytic lymphoma occurs more commonly than in the lymph node (A1-Bahrani et al., 1983; Lewin et al., 1978). The proportion of commonly occurring histologic types has varied accoring to various authors. Large cell lymphomas comprised the majority (53-60%) of gastrointestinal lymphomas in some studies (Fillipa et al., 1983; Lewin et al., 1978; Weingrad et al., 1982). In contrast, plasmacytoid small lymphocytic lymphoma was the most common histologic subtype of GIT and only 3% of cases belonged to large cell lymphoma in the study by Henry and Farrer-Brown (1977). In our study, large cell lymphomas outnumbered other histologic types which were less frequently but consistently noted.

Gastrointestinal lymphomas showed similar prognostic tendencies to nodal lymphomas (van Krieken et al., 1982; MacLennan et al., 1981; Otto et al., 1981; Park and Lee, 1991; Shepherd et al., 1988; Weingrad et al., 1982). Histologic types consisting of highly transformed lymphocytes including large cells, immunoblasts, and small noncleaved cells, had a poorer prognosis than small lymphocytic lymphoma, small cleaved cell lymphoma and mixed small cleaved and large cell lymphoma. The diffuse pattern also correlated with a poorer prognosis than the follicular pattern, as with nodal lymphomas (Hermann et al., 1980; Hui et al., 1988; Weingrad et al., 1982). However, in studies by Novak et al. (1979) and Lewin et al. (1978), cytologic type had no influence on patient survival. This may be related to the fact that the classification systems they used were those established prior to the Working Formulation. In our study, lymphomas with intermediate and high grade (82.1%) outnumbered those with low grade. This result agrees with that of MacLennan et al. (1981) but is not compatible with other studies (Otto et al., 1981; Weingrad et al., 1982) in which the proportions of low grade and high grade were similar.

Since gastrointestinal lymphomas have shown clinical and morphologic features distinctive from nodal lymphomas, many investigators have tried to explain these characteristics on the basis of histogenesis (Grody et al., 1985; Hey et al., 1990; Isaacson et al., 1989; Shepherd et al., 1988). With the advent of monoclonal antibodies reactive for specific lineage of tumor cells, the origin of the neoplastic cells can be more effectively addressed (Taylor, 1978).

The results of immunohistochemical studies attempting to clarify the lineage of neoplastic cells have been contradictory. In contrast to Isaacson et al. (1979 and 1983) demonstrating more than 50% of GIT lymphomas expressing histiocytic markers, B-cell lineage was predominant in other studies (Gray et al., 1982; van Krieken et al., 1982; Shepherd et al., 1988; Yamanaka et al., 1980). We could not identify any histiocytic expression in any of our lymphomas. This result is compatible with that of Grody et al. (1985).

In our study, 23 of 28 cases (82.1%) reacted with

B-cell markers and 3 cases (10.7%) with T-cell markers. Two cases (7.1%) did not react with either B-cell or T-cell markers. These results generally agree with those from western populations (Grody et al., 1985; Isaacson et al., 1987; Otto et al., 1981; Yamanaka et al., 1980). They confirm the fact that most GIT lymphomas are of B-lineage and that the majority of large cell lymphomas (histiocytic lymphoma) belong to B-lymphocyte lineage.

Among seventeen large cell lymphomas, three were of T-lineage and all occurred in the small intestine. All the lymphomas arising in the stomach (9 cases) and in the large intestine (3 cases) expressed B-lineage. These immunohistochemical results concur with those of other investigators (Grody et al., 1985; van Krieken et al., 1982; Shepherd et al.. 1988).

In our study, three cases of centrocytoid lymphomas were identified among 28 cases of GIT lymphomas. All of them were large cell lymphomas occuring in the stomach (1 case) and in the small intestine (2 cases). Van Krieken et al. (1982) insisted that there was no necessity to separate these lymphomas from the standard categories because these lymphomas did not differ from nodal lymphomas in either clinical or morphological aspects.

Recent study demonstrated that centrocytoid lymphomas lacked bcl-1 and bcl-2 rearrangement and expressed neither CD-5 nor CD-10 antigen (Wotherspoon et al., 1990; Isaacson et al., 1991). These findings suggested that centrocytoid lymphomas were distinct from centrocytic lymphoma and lymphomas of follicular center cell origin. However, in our study, the three cases of centrocytoid lymphomas were not cytomorphologically or immunophenotypically distinct from other gastrointestinal lymphomas. Hence, we feel that centrocytoid lymphomas should not be classified separately among the primary GIT lymphomas.

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