Colonoscopic Manifestations of Primary Colorectal Lymphoma

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Background and Study Aims: Little is known about the colonoscopic manifestation of colorectal lymphoma. This article describes the use of colonoscopy for diagnosis of primary colorectal lymphoma.

Patients and Methods: We analyzed colonoscopic findings in 13 retrospectively collected cases of primary colorectal lymphoma diagnosed between 1990 and 1999 at our hospital.

Results: The primary colorectal lymphomas were distinguished into three colonoscopic types: a) the mucosal type, which included six lymphomas (46%), which were classified into two subtypes, erosive (two lymphomas) and ulcerative (four lymphomas); b) the polypoid type, which included three lymphomas (23%); and c) the

massive type, which included four (31%). The proportion of patients with T-cell lineage lymphoma (5 of 12, 42%) was higher than in previous studies. Three cases were diagnosed as enteropathy-associated T-cell (EAT)-like lymphoma: one presenting with multicentric ulcerations, one as a massive type and another as a polypoid type. Of those with B-cell lineage lymphoma (7 of 12, 58%), three presented as massive type, two as polypoid type and two as erosive subtype.

Conclusions: Based on the analysis of colonoscopic records, we have proposed three main types of primary colorectal lymphoma. An unusually high proportion of T-cell lineage lymphomas was noted, but as the number of cases was low, further study is still needed for confirmation.

Introduction

Primary colorectal lymphoma is relatively rare, representing approximately 0.05% of all colorectal neoplasms [1]. Roughly 15% of patients with known lymphoma have clinical evidence of gastrointestinal involvement [2], and the commonest regions affected are the stomach and the small bowel. Only about 10% of those patients with gastrointestinal lymphoma have disease affecting the colon [3,4].

In primary colorectal lymphoma, early diagnosis is important if a surgical cure is to be achieved. Colonoscopy is an important method in the diagnosis of colorectal disease, but little is known of its value in colorectal lymphoma diagnosis. The purpose of this study is to evaluate this technique through a colonoscopic assessment of 13 patients with clinicopathologically proven primary colorectal lymphoma.

Patients and Methods

Primary colorectal lymphoma was defined following the criteria of Dawson et al. [5]. Between January 1990 and October 1999, 13 patients whose disease met the criteria of primary colorectal lymphoma received colonoscopic examination at the National Taiwan University Hospital. These patients were also regularly followed up except for patient 7 who had only a 5-month follow up. The demographic and clinical information collected on each patient included age, sex, clinical presentations, colonoscopic manifestations, histopathologic diagnosis, clinical stage, treatment and outcome. Patients with Hodgkin's disease were excluded from this study.

Tissue specimens from biopsy and/or surgical resection of the colorectum were fixed in formalin and embedded in paraffin. Sections were stained with hematoxylin-eosin and with monoclonal or polyclonal antibodies using previously described methods [6]. The antibodies used in this study and their commercial sources were as follows: CD3, CD5, CD8, CD15, CD20, CD30, CD43, CD45RB, and CD45RO (Dako, Glostrup, Denmark) and CD56 (Novocast, Newcastle, UK). Lymphomas were classified according

to the Revised European-American Lymphoma (REAL) classification of the International Group [7], and staged using the Musshoff modification of the Ann Arbor system for gastrointestinal lymphoma [8].

Results

Clinical Presentation

The study included nine men and four women, with a median age of 54 years at disease onset (Table 1). Five of them (38%) presented with passage of bloody stools, six (46%) with abdominal pain, three (23%) with watery diarrhea, three (23%) with body weight loss, and one (8%) with abdominal fullness. Two patients (15%) had a history of inflammatory bowel disease, ulcerative colitis, and no patient had a history of colon cancer or human immunodeficiency virus (HIV) infection.

Site of Involvement

Sites of involvement included the ascending colon in three cases (23%), the rectosigmoid colon in two (15%), the cecum in two (15%), the transverse colon in one (8%), and

multicentric or diffuse involvement in five instances (38%).

Colonoscopic Manifestation

We analyzed the colonoscopic images and classified them into three main categories as follows: 1) mucosal type; 2) polypoid type; and 3) massive type. Table 2 shows the distributive correlation of colonoscopic types and immunophenotypes.

Mucosal Type

This type presented in 46% of cases (6/13), and was classified into two subtypes. The erosive subtype (2/6; both B-cell lineage lymphomas) was characterized by small (less than 5mm), superficial erosive, hyperemic, edematous changes within the mucosal layer, not extending beyond the mucosae muscularis. The ulcerative subtype (4/6; three of these were T-cell lineage lymphomas) is characterized by large (more than 5mm), deep (penetrating the mucosae muscularis or just even with the submucosa) ulcerative lesions and by hyperemic, edematous changes.

Table 1 Colonoscopic and histological features, treatment and survival in 13 patients with primary colorectal lymphoma

Patient No.	Sex	Age at time of diagnosis	Colonoscopic type	Location	CFS diagnosis*	Stage†	Histology‡	Treatment	Survival from time of diagnosis, months
1	F	47	Ulcerative	Multicentric	Ulcerative colitis	EI2	PTCL	Surgery	10 (dead)
2	M	47	Polypoid	Rectum	Lymphoma	EII1	PTCL	Surgery + chemotherapy	6 (dead)
3	M	70	Polypoid	Cecum	Tubular adenoma	EI2	DLBL	Surgery + chemotherapy	8 (dead)
4	M	28	Massive	Ascending colon	Cancer	EII1	ENK/TL	Surgery + chemotherapy	54 (alive)
5	M	82	Massive	Cecum	Cancer	EII1	DLBL	Surgery + chemotherapy	9 (dead)
6	M	58	Polypoid	Ascending colon	Lymphoma	EI1	MALToma	Polypectomy	38 (alive)
7	M	86	Massive	Transverse colon	Cancer	EIV	DLBL	Chemotherapy	5 (alive)
8	F	42	Ulcerative	Multicentric	Colitis	EI2	PTCL	Chemotherapy	6 (dead)
9	F	42	Massive	Ascending colon	Cancer	EII1	DLBL	Chemotherapy	23 (dead)
10	M	27	Erosive	Rectum	MALToma	EI1	MALToma	No specific treatment	78 (alive)
11	M	38	Ulcerations	Multicentric	Lymphoma	EIV	PTCL	Surgery	1 (dead)
12	M	57	Erosive	Multicentric	Ulcerative colitis	EI2	MALToma	Chemotherapy	60 (dead)
13	F	27	Ulcerative	Multicentric	Lymphoma	EI2	DLL	Surgery + chemotherapy	114 (alive)

* CFS diagnosis means initial colonoscopic impression.

† According to the Musshoff modification of the Ann Arbor system for gastrointestinal lymphoma [8].

‡ REAL classification: PTCL, peripheral T-cell lymphoma, unspecified; DLBL, diffuse large B-cell lymphoma; ENK/TL, extranodal NK/T-cell lymphoma; MALToma, extranodal marginal zone B-cell lymphoma of MALT (mucosa-associated lymphoid tissue) type, low-grade; DLL, diffuse large-cell lymphoma, unspecified.

Table 2 Distributive correlation of colonoscopic types and immunophenotypes

	Mucosal Erosive	Ulcerative	Polypoid	Massive	Total
T-cell	0	3	1	1	5 (42 %)
(PTCL	0	3	1	0	4)
(NK/T	0	0	0	1	1)
B-cell	2	0	2	3	7 (58 %)
(DLBL	0	0	1	3	4)
(MALT	2	0	1	0	3)
Unknown	0	1	0	0	1
Total	2 (15 %)	4 (31 %)	3 (23 %)	4 (31 %)	13 (100 %)

Patient 10 presented with bloody diarrhea. Colonoscopic images showed erosive inflammatory change in the rectum (Figure 1a), which at biopsy proved to be low-grade extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type.

Patient 11 presented with chronic diarrhea for 6 months followed by bloody diarrhea and fever. Colonoscopic images revealed multiple ulcerations over the entire colon (Figure 1b) which at biopsy proved to be peripheral T-cell lymphoma, of unspecified type.

Polypoid Type

This type presented in 3/13 (23%) cases, of which two were B-cell lineage and one was a T-cell lineage lymphoma. It was identified as a wide-based sessile or pedunculated lesion, having a gradually sloping contour and a smooth or granular, erosive surface. Patient 6 presented with bloody diarrhea. Colonoscopy revealed multiple polypoid lesions throughout the ascending colon (Figure 1c). The patient underwent polypectomy and a low-grade extranodal marginal zone B-cell lymphoma of MALT type was confirmed.

Massive Type

This type presented in 4/13 (31%) of cases; three were B-cell lineage and one was a T-cell lineage lymphoma. It was identified as a intraluminal protruding, lobulated neoplastic lesion with or without ulceration. Patient 7 presented with abdominal pain and body weight loss. Colonoscopy revealed an annular protruding, lobulated mass in the transverse colon (Figure 1d) which at biopsy proved to be a diffuse large B-cell lymphoma.

Histopathological and Immunohistochemical Study

The histological findings are summarized in Table 1. In patients 3, 5, 7, and 9 (31%), diffuse infiltration by large B-cell lineage lymphoma cells was shown and was classified as diffuse large B-cell lymphoma (DLBL).

In patients 6, 10 and 12 (23%), infiltration by monotonous centrocyte-like cells and frequent lymphoepithelial lesions were shown, a picture similar to that seen in gastric low-grade B-cell lymphoma of MALT type. The three patients were diagnosed as having low-grade extranodal marginal B-cell lymphoma of MALT type, on the basis of lymphocytes positive for CD20 and negative for CD3, CD5 and CD56.

In patients 1, 8 and 11 (23%), the lymphomas were classified as peripheral T-cell with enteropathy-associated T-cell lymphoma (EATL)-like appearance, characterized by the infiltration of pleomorphic small to medium-sized lymphoid cells admixed with large cells with irregularly folded nuclear membrane and prominent intraepithelial lymphocytosis (Figure 2). Immunophenotypically, these lymphoid cells were positive for CD3, CD45RO and negative for CD8, CD20, CD30, and CD56.

In patient 2, the lymphoma was classified as peripheral T-cell lymphoma, of unspecified type, based on exclusion criteria in the REAL classification.

Patient 4 had diffusely pleomorphic medium-to-large lymphoid cell proliferation, with coagulative necrosis but no angiocentrism. Immunophenotypically, cells were positive for CD3 (cytoplasmic), CD43, CD45RO, and CD56, and negative for CD8 and CD20. The cells were EBV-positive by *in situ* hybridization. Thus, the patient was diagnosed as having extranodal NK/T-cell lymphoma.

Patient 13 had a diffuse large-cell lymphoma. Immunophenotypic evaluation was unavailable as the specimen was very small.

Overall, in 58% of cases the lymphomas were B-cell lineage and in 42% they were T-cell lineage.

Clinical Stage, Treatment and Outcome

Two patients had stage EI1 disease, five stage EI2 disease, four stage EII1, and two stage IV disease.

Seven patients underwent surgical treatment, and five of these received adjuvant chemotherapy with a regimen which included cyclophosphamide, vincristine, doxorubicin and prednisolone (CHOP). Three patients (cases 2, 3 and 5) responded to treatment but their disease recurred later. Two patients (cases 4 and 13) responded to treatment and obtained complete remission. Another two patients (cases 1 and 11) received surgical treatment only and soon died of hemophagocytosis. Among the four patients (30%) who received chemotherapy only, the response in patient 7 was partial; that in patient 9 was complete initially, but there was a recurrence 6 months later; there was a refractory response in patient 12; and that in patient 8 was complicated by sepsis. One patient (case 6) underwent colonoscopic polypectomy only and had no recurrence during the

Figure 1 Colonoscopic appearances of primary colorectal lymphomas.

a A mucosal erosive subtype (patient 10) shows a low-grade extra-nodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type in the rectum.

b A mucosal ulcerative subtype (patient 11). The ulceration extends over the ascending colon and sigmoid colon. **c** A polypoid type (patient 6) located at the ascending colon. **d** A massive type (case 7) located at the transverse colon

Figure 2 Histopathological image, from patient 11, showing medium-sized lymphoid cells admixed with some large cells with irregularly folded nuclear membranes (hematoxylin & eosin, $\times 400$)

following 5 years. Patient 10 received neither surgery nor chemotherapy.

In our series, the 5-year-survival rate was only 20%, and the survival curves differed between B-cell and T-cell lineage lymphomas and between colonoscopic types or subtypes, but the differences were not statistically significant.

Discussion

Primary colorectal lymphoma is a rare entity, representing fewer than 1% of large bowel malignancies [3]. However, increasing numbers of cases are being reported in homosexual individuals in association with the acquired immune deficiency syndrome (AIDS) [9]. Most reports of gastrointestinal lymphomas indicate a predominance of B-cell disease, and few studies have dealt with gastrointestinal lymphomas of the colon and rectum. Because the frequency of B-cell lymphoma in the Western countries is higher than in the Far East [10,11], the clinical features and outcomes may be different in these areas.

In one study from Taiwan, five out of sixteen cases (31%) of primary colorectal lymphomas were of T-cell origin [12]. In Japan, where human T-cell lymphotropic virus type I (HTLV-1) infection is endemic, some cases of HTLV-1-associated primary T-cell gastrointestinal lymphoma have been reported [13]. Interestingly, in our study, five cases (42%) had a T- or NK-lineage, a much higher percentage than reported previously [14]. Peripheral T-cell and NK-cell lymphomas are uncommon in Western populations, in contrast to findings in oriental countries. The reason (ethnic or epidemiological) for this difference is unknown.

In Western countries, EATL is the most common primary gastrointestinal T-cell lymphoma. In our study, only three lymphomas (in patients 1, 8, and 11) were classified as EATL-like peripheral T-cell lymphomas.

It is found in the literature that the prognosis for gastrointestinal T-cell lymphoma is worse than for B-cell lymphoma. Less than 25% of patients with T-cell lymphoma survived for 5 years, and more than half of them died within 6 months [12,15,16]. In our series, the long-term survival associated with T-cell lymphoma was poorer than that with B-cell lymphoma, although the difference was not statistically significant. We need to examine more cases and to have further follow up.

Our conclusion from this study is that there are four important colonoscopic types or subtypes of primary colorectal lymphoma: a mucosal erosive subtype, a mucosal ulcerative subtype, a polypoid type, and a massive type. An unusually high proportion of cases, i.e. 42%, were T-cell lineage lymphomas. Our study may offer a new colonoscopic diagnostic concept for primary colorectal lymphoma. The number of patients in this study is low, and we still need further prospective studies to clarify this disease entity.

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