Non-Hodgkin's Lymphomas of the Colon

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Abstract

Background: Non-Hodgkin's lymphoma of the colon is a rare and consequently poorly studied extranodal lymphoma. Most of the previous publications used old pathologic classifications and old diagnostic and treatment approaches.

Objective: To examine the clinical presentation, pathologic classification, treatment and outcome of patients with NHL of the colon.

Methods: A retrospective study was performed of all patients with NHL and involvement of the colon in two medical centers. The patient group consisted of 17 patients over a 13 year period.

Results: Fourteen patients had primary involvement and 3 secondary. The ileocecal region and cecum were the most frequent sites of involvement, occurring in 76% of patients. Most patients had bulky disease: three had a diameter > 5 cm and eight a diameter > 10 cm. Aggressive histology was found in 12 patients: diffuse large B cell lymphoma in 11 and peripheral T cell lymphoma in 1. Three patients had mantle cell lymphoma and two had indolent lymphomas: mucosa-associated lymphoid tissue (n=1) and small lymphocytic (n=1). Eleven patients underwent hemicolectomy: right sided in 9 and left sided in 2, and 5 DLBCL patients required emergency surgery for intestinal perforation. The median overall survival was 44 months (range 1–147). Disease stage influenced prognosis; six of seven patients with limited-stage DLBCL who received aggressive chemotherapy achieved complete remission and enjoyed prolonged survival, whereas patients with aggressive disseminated disease had resistant disease and poor survival (median 8 months).

Conclusions: Most colonic lymphomas are aggressive B cell lymphomas. Diagnosis is often delayed. Early diagnosis may prevent perforation. Those with limited-stage disease when treated with aggressive chemotherapy may enjoy prolonged survival. The role of elective hemicolectomy to prevent perforation should be examined in prospective trials.

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Lymphoma of the colon is a rare and consequently poorly studied form of extranodal lymphoma. At least one-fourth of non-Hodgkin's lymphomas are probably of extranodal origin [1]. The gastrointestinal tract is the most frequently involved site, accounting for 30–40% of all extranodal cases and approximately 4–20% of all NHL [2-3]. The stomach is the most common location of gastrointestinal lymphomas, representing 51–86% of cases, followed by the small intestine. Only 6–14% of gastrointestinal lymphomas are reported to be in the colon [4-8]. Colon lymphomas comprise only 1.2% of all cases of colon cancers [9]. Due to the rarity of the condition, most of the data published in the western world on lymphomas of the colon are based on case reports and small series of up to 35 patients. Most of the reports in the literature were published before the appearance of the Revised European-American Lymphoma classification [10] and the recent World Health Organization classification [11], which for the first time included specific entities for extranodal lymphomas and the entity of mantle cell lymphoma. Data are lacking on the clinical spectrum, histology, treatment and outcome. We present a retrospective analysis of our experience with patients suffering from lymphoma involving the colon.

Patients and Methods

The NHL patient registries at the institutes of Hematology at Rabin Medical Center (Beilinson Campus) and Shaare Zedek Medical Center were reviewed for all patients with lymphoma involving the colon. Clinical and laboratory data were retrieved from the hospital databases for analysis. None of the patients was known to have previous inflammatory bowel disease, positive serology for human immunodeficiency virus, or HIV infection.

Results

Patients' characteristics [Table 1]

Seventeen patients were identified over a 13 year period, comprising 1.4% of the total NHL registry. Since regular lymphoma evaluation was performed, only symptomatic patients were diagnosed and the true incidence of lymphoma of the colon is probably higher. The male/female ratio was 2.4:1, and the median age at diagnosis 72 years (range 23–82 years). Fourteen patients had primary intestinal lymphoma, and in 3, colonic involvement occurred at relapse or progression. The most common presenting symptoms were abdominal pain in 10 patients (56%), changes of bowel habits in 6 (35%), and weight loss in 5 (29%). The mean duration of symptoms before diagnosis was 2.8 months (range 0–7 months). Five patients with diffuse large B cell lymphoma presented with an acute abdomen due to perforation of the intestine requiring emergency surgery.

Seven patients presented with localized stage I/II disease. All had DLBCL. Ten patients presented with disseminated stage IV

NHL = non-Hodgkin's lymphoma
DLBCL = diffuse large B cell lymphoma

HIV = human immunodeficiency virus

Table 1. Clinical features

Patient no.	Gender	Age (yrs)	Pathology	Location	Stage	Bulky (cm)	Elevated LDH	IPI	Colectomy	Perforation	Chemotherapy agents	Response	Overall survival (mos)	Outcome
1	M	72	DLBCL	Ileocecal	I	> 10	No	1	Yes		Rituximab-CHOP	CR	6	Alive
2	F	67	DLBCL	Ileocecal	IV	> 10	Yes	5	Yes	Yes	CEPP	NR	11	Died
3	M	77	DLBCL	Sigmoid	IV	> 10	Yes	4	Yes	Yes	Rituximab-CHOP	NR	12	Died
4	F	79	DLBCL	Ileocecal	IV	> 10			Yes		None*		2	Died
5	M	77	DLBCL	Ileocecal	I	> 5	No	1	Yes		CNOP, Irradiation	CR	96	Died
6	M	23	DLBCL	Ileocecal	II	> 10	Yes	1	Yes		MACOP-B	CR	147	Alive
7	F	65	DLBCL	Cecum	I	> 10	No	1	Yes		CHOP	CR	73	Alive
8	M	52	DLBCL	Sigmoid	I	No	No	1	Yes	Yes	CHOP	CR	121	Alive
9	M	64	DLBCL	Ileocecal	II	No	No	1	Yes	Yes	CHOP	CR	10	Died
10	M	66	DLBCL	Ileocecal	I	> 5	Yes	2	Yes		CHOP	PD	5	Died
11	M	82	DLBCL	Cecum	IV	> 10	Yes	5	Yes	Yes	None*		1	Died
12	M	66	Peripheral T cell lymphoma	Cecum	IV	No	Yes	5	No		CHOP	PD	3	Died
13	F	66	MCL	Cecum	IV	No	Yes	4	No		Oral	PR	6	Died
14	M	75	MCL	Colorectal	IV	No	No	3	No		CHOP	CR	62	Died
15	M	73	MCL	Ileocecal	IV	No	Yes	3	No		CHOP	CR	34	Died
16	M	72	MALT	Cecum	IV	> 5	No	3	No		Chlorambucil prednisone	NR	44	Died
17	F	81	SLL	Sigmoid	IV	> 10	Yes	4	No		CHOP	CR	75	Alive

* Died postsurgery

DLBCL = diffuse large cell lymphoma, MALT = mucosal associated lymphoid tissue, MCL = mantle cell lymphoma, LDH = lactate dehydrogenase, SLL = small lymphocytic lymphoma, IPI = International Prognostic Index, CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone, CEPP = cyclophosphamide, etoposide, procarbazine, prednisone, CNOP = cyclophosphamide, mitoxantrone, vincristine, prednisone, MACOP-B = methotrexate, adriamycin, cyclophosphamide, vincristine, prednisone, bleomycin, CR = complete remission, PR = partial remission, NR = no response.

disease with up to five extranodal sites of involvement (including other intestinal areas, spleen, liver, orbit, bone marrow, central nervous system, lung, trachea, skin and bone). Lymphadenopathy was present in 11 patients – in abdominal sites in 10 and the mediastinum in 5. Bone marrow involvement was infrequent and occurred in only two patients. All patients with T cell lymphoma, mantle cell lymphoma, mucosa-associated lymphoid tissue lymphoma, and small lymphocytic lymphoma presented with a disseminated stage IV disease.

Eleven patients had bulky disease. In three patients the diameter was more than 5 cm and in eight over 10 cm. The tumor mass was palpable at diagnosis in eight patients. Anemia was present in 10 patients (57%) and 9 patients had high serum levels of lactic dehydrogenase. Serum beta-2 microglobulin levels were measured in seven patients and were elevated in all of them. The International Prognostic Index score was low in six patients, intermediate in four and high in six.

Histology and distribution

Diagnosis was established by colectomy in 11 patients and by colonoscopy with biopsy in the remaining 6. The lesion appeared ulcerative in seven patients, polypoid in four patients, nodular in one and flat in one. Ninety-four percent were of B cell origin; 88% had aggressive histology: DLBCL in 11, MCL in 3, and peripheral T cell lymphoma in 1. Two patients had indolent lymphomas: MALT in one and small lymphocytic lymphoma in the other. In the 6 patients with DLBCL in whom Ki-67 proliferation index was measured, it was very high (85–90%). The most frequently involved site at diagnosis was the ileocecal region in 8 patients (47%), followed by the cecum in 5 (29%), the sigmoid in 3 (18%) and the colorectal area in 1 patient (6%).

Treatment and outcome

Nine patients underwent right hemicolectomy, one left hemicolectomy and one sigmoidectomy. In five patients this was an emergency procedure due to intestinal perforation that occurred at diagnosis before treatment. Their histology was DLBCL and only one remained alive after 1 year of follow-up. Two patients (age 79 and 82 years) died from post-surgical complications following right hemicolectomy before receiving treatment.

Thirteen patients were treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-like combination chemotherapy. One patient refused further chemotherapy and received local irradiation. Nine (69%) achieved a complete remission. With a median follow-up of 75 months (range 6–147), 5 patients are still in complete remission for 6, 73, 75, 121 and 147 months. Four patients did not respond to therapy and died from resistant usually disseminated disease 3, 5, 11 and 12, months

MCL = mantle cell lymphoma

MALT = mucosa-associated lymphoid tissue

after diagnosis. Two patients received oral therapy: one who had relapsed stage IV MCL achieved a short-term partial remission on combination oral therapy and died 6 months from diagnosis of colonic lymphoma; the second patient with stage IV MALT did not respond to chlorambucil and prednisone and died 44 months after diagnosis. The median overall survival was 44 months (range 1–147 months). This median was distinctly shorter for those who had perforated intestine: 11 months (range 1–121) compared to 44 months (range 2–147) for those who did not.

In patients with DLBCL disease, stage at diagnosis influenced prognosis. Six of seven patients with limited-stage disease (stage I and II) who received aggressive chemotherapy achieved complete remission. Four of them demonstrated very prolonged disease-free survival (73, 96, 121, 147 months). One died of lung cancer while in complete remission, and another has a short follow-up (6 months). Patients with disseminated stage IV disease (n=4) demonstrated poor survival (median survival of 8 months).

Discussion

The colon is an uncommon site of involvement in non-Hodgkin's lymphoma. The most common symptoms of colonic lymphoma are abdominal pain and weight loss, with a palpable abdominal mass identified on physical examination in half the patients. By far the most common sites of involvement are the ileocecal region and cecum. In this series of 17 patients these were the predominant sites involved, accounting for 76% of the patients. Only four patients had disease in the left colon/rectum area. Most cases were aggressive lymphomas and all except one were of B cell origin. The most common presenting symptoms were abdominal pain, altered bowel habits and weight loss that lasted in some patients for months before diagnosis. Some patients were asymptomatic until the occurrence of an acute abdomen due to intestinal perforation. At diagnosis the lymphoma was bulky in 65% of the patients, reaching over 10 cm in 47%, implying a delay in diagnosis with a possibly adverse effect on prognosis. The lack of specific complaints and the rarity of intestinal obstruction probably accounts for the delay in diagnosis. These bulky masses can usually be palpated by simple physical examination and viewed by ultrasonography.

Five patients had intestinal perforation, two of whom were symptomatic for 7 months before the diagnosis. Emergency hemicolectomy was performed in all five but only one attained a prolonged survival. Four died within 12 months, raising the question of whether earlier diagnosis could prolong survival.

Auger and Allan [12] reported that the most common presenting symptoms in their series of 22 patients with primary iliocecal lymphoma were abdominal pain, altered bowel habits and weight loss. An abdominal mass was palpable in 50%. Zighelboim and Larson [4] analyzed their 19 year experience at the Mayo Clinic and found that the most common site of involvement was the cecum, found in 73% of patients, followed by the rectum. Doolabh and colleagues [8] reported similar rates of cecum involvement and found that the lack of specific symptoms delayed diagnosis by 1–12 months.

In this report colon lymphoma was more frequent in men. Koch and team [5] studied the clinical features of 371 primary gastrointestinal NHL patients. They found that the ileocecal region was involved in 7% of the cases, the colon region in 0.8% and the rectal region in 1.6%. They also found predominance of male gender in patients with NHL in the ileocecal region (2.7:1). Most of the lymphomas were of aggressive type. Five year survival was 76% and was similar to survival in gastric lymphomas. This rate was significantly higher than in patients with small intestine lymphoma.

Ileocecal NHL, like gastric lymphoma, can be diagnosed by endoscopy, raising the question of whether surgery is really necessary for cure. It is now known that gastric lymphomas rarely perforate and their prognosis depends on lymphoma-related factors and not on surgical treatment. However, it is still thought that the prognosis of intestinal lymphomas is related to surgery; therefore, it seems appropriate and cautious to resect intestinal lymphomas whenever possible [13,14]. Most patients in our cohort underwent surgery followed by combination chemotherapy. Only patients attaining complete remission had prolonged survival. Stage at diagnosis appeared to be an important prognostic factor. When the lymphoma was localized at diagnosis, combination chemotherapy led to prolonged survival and possibly cure. When lymphoma was disseminated at diagnosis the prognosis was poor.

Since most of the patients underwent colectomy, we cannot make any definitive statement on the role of colectomy in the treatment of colonic lymphoma. Since the rate of spontaneous perforation in patients with DLBCL was high (5 of 11, 45%), it may be beneficial to prevent perforation when possible by performing an elective hemicolectomy upon diagnosis. On the other hand, it is possible that similar to gastric lymphoma, early diagnosis and systemic chemotherapy may prevent the occurrence of perforation and the need for hemicolectomy.

The optimal therapy for colon lymphomas has never been determined by prospective randomized clinical trials. Large prospective studies involving multiple centers are needed before we can recommend firm guidelines regarding the necessity of surgical resection of colon lymphoma and the duration of chemotherapy for stage I disease.

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