ORIGINAL PAPERS

Primary lymphoma of the colon

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ABSTRACT

Background: primary colorectal lymphoma is a very rare disease, representing less than 0.5 % of all primary colorectal neoplasms. The gastrointestinal tract is the most frequently involved site of all extranodal lymphomas, the most common type of that is non-Hodgkin's lymphoma. Early diagnosis is often difficult because of unspecific symptoms. Therapeutic approaches have classically included radical resection, chemotherapy and radiotherapy.

Materials and methods: we present our experience in the management of primary colorectal lymphomas over a 17-year period (1994-2011).

Results: in this period 7 cases of primary colorectal lymphoma were diagnosed in our institution. Abdominal pain and change in bowel habit were the most frequent symptoms. Five patients underwent emergency surgery because of bleeding or bowel obstruction. All primary intestinal lymphomas studied were of the B-cell phenotype. Patients were followed up for a median of 59 months (range 1-180). Three of them are alive with no evidence of recurrence.

Conclusion: combination treatment with chemotherapy and surgery can obtain good remission rate. Surgery can resolve complications such as bleeding or intestinal perforation that are implicated in lymphoma mortality.

Key words: Lymphoma. Colon. Surgery. Treatment.

INTRODUCTION

Primary lymphoma of the colon and rectum is a rare tumor. It comprises only 0.2-1.2 % of all colonic malignancies (1,2). The gastrointestinal (GI) tract is the most frequently extranodal involved site, accounting for 30-40 % of all cases (1,3). The predominant location of GI lymphomas is the stomach (50-60 %) (4) followed by small bowel (20-30 %), and colon and rectum (10-20 %) (5). To establish the diagnosis it is necessary to have a high index of suspicion because of the variability of symptoms.

Treatment often involves a multidisciplinary approach, combining surgery and chemotherapy, with the use of radiotherapy in selected cases. However, there are no randomized trials and treatment decisions are mainly based on expert opinions or consensus.

We present the experience of primary colorectal lymphomas over a 15-year period in a single center.

PATIENTS AND METHODS

We performed a retrospective descriptive study of all consecutive cases of primary colorectal lymphoma diagnosed in our institution from 1994 to 2011. The registry of the Department of Pathology was used for this purpose.

All cases were histologically confirmed. The type of lymphoma was classified according to the WHO classification system (6). Immunohistochemical analysis (IHC) was performed to classify lymphomas as germinal center B-cell (GCB) or non-germinal center B-cell (ABC) subtypes (7). A computed tomography scan (CT) and a bone marrow biopsy was performed to determine what stage of the Ann Arbor Staging System for gastrointestinal lymphoma was used.

The following clinical information was obtained: Age, sex, presentation, site of tumor, operation performed, his-

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tology, length of stay, intraoperative complications, adjuvant therapy, treatment response and duration of follow-up.

RESULTS

During the 15-year study period, 7 cases of primary colorectal lymphoma were diagnosed. This comprised 0.23 % of all colorectal malignances seen in our department during this period (Table I).

The median age at diagnosis was 67 years (range: 35-87), 4 males. Five patients had good performance status (ECOG/PS 0-1). All of the patients were stage I-II according to Ann Arbor Staging System. The International Prognostic Index (IPI) was low (0-1) in 4 cases. The patients presented with different symptoms, including abdominal pain in 5, change in bowel habit in 4, bleeding in 3, and anorexia or loss of weight in two cases (29 %).

The most common sites of involvement were sigmoid colon in 3, cecum in 2 and ascending colon in 2 other cases. Macroscopically the lesions varied from solitary fungating masses to multiple colonic polyps (Fig. 1). All primary colorectal lymphomas studied were B-cell type (Fig. 2), staining positively for pan B-cell marker CD20. Moreover, 6 out of 7 of the cases corresponded to diffuse large B-cell lymphoma

(DLBCL). There was one case of follicular lymphoma. According to immunohistochemical analysis, DLBCL cases

Fig. 1. Sigmoid resection specimen with fungating masses corresponding with lymphoma.

Table I. Summary of patients with primary colon lymphoma diagnosed in our institution

No.	Age	Sex	Presentation	Site	Operation	Histology	Immunohistochemical analysis	Stage	Surgery	Chemo	RT	Follow up	Exitus
1	88	Female	Bleeding	Sigmoid colon	Hartmann procedure	DLBCL	GCB	IAE	Elective	ND	ND	Postoperative exitus	Yes
2	84	Male	Pain, change in bowel habit, intestinal obstruction	Sigmoid colon	Hartmann procedure	DLBCL	ABC	IAE	Emergency	ND	ND	Paliative treatment one year after surgery	Yes
3	52	Male	Pain, LOA, LOW, change in bowel habit, intestinal obstruction	Sigmoid colon	Rectal anterior resection	DLBCL	ABC	IAE	Elective	ND	ND	Postoperative exitus	Yes
4	29	Male	Pain	Cecum	Right hemicolectomy	DLBCL	Not done	IAE	Emergency	COP	Yes	> 15 years	No
5	71	Female	Pain, change in bowel habit	Ascending colon	Endoscopic biopsy	Follicular lymphoma	GCB	IIAE	ND	COP	No	9 years, extracolonic recurrence RCHOP	Yes
6	85	Female	Pain, change in bowel habit, bleeding	Ascending colon	Right hemi-colectomy	DLBCL	GCB	IAE	Emergency	Rituximab	No	3 months	No
7	73	Male	Bleeding	Cecum	Endoscopic biopsy	DLBCL	ABC	IAE	ND	RCHOP	Yes	4 months	No

LOA: Lost of appetite. LOW: Lost of weight. DLBCL: Diffuse large B-cell lymphoma. GCB: Germinal centre B-cell-type. ABC: Activated B-cell type. ND: Not done. COP: Cyclophosphamide, vincristine and prednisone. RCHOP: cyclophosphamide, vincristine, prednisone doxorubicine and rituximab.

could be subclassified as GCB subtype in 2 cases and as ABC subtype in 3. In one case the paraffin block was not available for additional immunohistochemical studies.

The diagnosis of lymphoma was done by surgical resection in 5 patients, and by endoscopic biopsies in 2.

Two patients underwent elective resection and 3 other patients required emergency surgery. Of these, two patients presented with lower gastrointestinal bleeding requiring right hemicolectomy and one patient with intestinal obstruction underwent a Hartmann's procedure. There were two post-operative exitus, a patient with an elective anterior rectal resection who died due to an anastomotic leak and another patient having emergency surgery who died of respiratory and renal failure.

Four patients received chemotherapy or immunotherapy, 2 after surgical excision and 2 after endoscopic diagnosis. The regimens used were cyclophosphamide, vincristine and prednisone (COP), plus doxorubicine (CHOP) or/and rituximab (R). This last is a monoclonal antibody against the protein CD20 that destroys B cells and is part of the so call immunotherapy. This follow-up was performed jointly with the medical oncologists-hematologists. All of them achieved complete remission. The follow-up of the four patients had a median of 52 months (range 1-180). Three patients are alive with no evidence of recurrence and 1 patient died of systemic lymphoma progression. Interestingly, this patient had follicular lymphoma.

DISCUSSION

Primary colorectal lymphoma is a rare disorder comprising 0.1 %-0.5 % of all malignant tumor of the colon and rectum (8,9).

The disease appears later in life, predominantly in the male population (2,10-11). In our study, the mean age was 67 years, which is similar to what was reported in the literature, although we report a case of a 29 years old woman, the youngest patient ever presented in previous series. However, in our study, we have found a similar distribution between males and females.

In our patients, the most common presenting symptom was abdominal pain, according to previous reports (2,5,12,13). Other less common modes of presentation in our series included; change in bowel habit, gastrointestinal bleeding and anorexia or loss of weight, similar to other studies published (5); (1,2,10). Some authors have reported rare cases of emphysematous colitis (14) as the first clinical manifestation, and also masquerading Crohn's disease (15). In conclusion, there are nonspecific symptoms and the diagnosis may be delayed for extended periods.

The most common site for colorectal lymphoma is the cecum, occurring in 57 % of cases, probably because more lymphoid tissue is present in this region. Other sites of the disease are the ascending colon (18 %), the transverse and recto-sigmoid colon (10-20 %) and the descending colon (5 %) (2,12,13,16,17). However, in our study, the most

common location for colorectal lymphoma was the sigmoid colon (43 %).

All of our tumours were of B-cell origin, most of them diffuse large B-cell types (85.7 %); this again correlated well with previous reports (2,18). Inflammatory bowel disease (IBD) and immunosuppression have been reported as classical risk factors (19). Even more, human immunodeficiency virus (HIV) positivity has been reported to be associated with a higher incidence of anorectal lymphomas (3). However recent studies (2,5) have not established them as clear risk factors. None of the patients in this series had IBD, HIV or other immune disorders, so we cannot establish a direct causal link.

Treatment of colorectal lymphoma usually involves surgery and chemotherapy. Nowadays, due to the introduction of new active drugs as monoclonal antibodies like rituximab as part of chemotherapy treatment (20), the role of surgery is debatable. Some authors propose that surgery could be beneficial to prevent perforation or bleeding (1) whereas others suggest that early diagnosis and chemotherapy might avoid a surgical procedure. In our opinion, surgery may be beneficial in those patients at risk of complications such as hemorrhage, obstruction and perforation, but it should be associated with postoperative chemotherapy. Moreover, surgery alone with or without radiotherapy must be reserved for selected cases, as localized low-grade lymphomas, because the vast amount of lymphomas, moderate and high-grade B cell lymphoma as DLBCL, almost always extends beyond local fields. In these cases, chemotherapy, with or without surgical excision remains the basis of the treatment.

As known, the CHOP chemotherapeutic regimen (cyclophosphamide, doxorubicine, vincristine and prednisone) remains the first line therapy for primary colorectal lymphomas. Several prospective trials have shown that adding rituximab, monoclonal antibody, to CHOP regimen (RCHOP) resulted in higher response rates and better survival in systemic non-Hodgkin lymphomas but there is few information in primary colorectal lymphoma (21). There are some series that

Fig. 2. High power view of bowel lymphoma of the colon.

have shown their experience with chemotherapy, many of them before rituximab era, but their results are controversial (22). Of interest, in our study, four patients were treated with chemotherapy or immunotherapy, two of them with previous hemicolectomy and all patients achieved complete response.

Recent advances in gene expression profiling and immunohistochemical analysis (IHC) have led to the identification of different subtypes of DLBCL, and confirmed that patients with the ABC disease subtype are less likely to respond well to CHOP-based regimens than those with GCB disease (23). In the future, the identification of these patterns could predict the most effective management strategies for patients. There are no series of patients published with the IHC analysis and survival correlation. In our series, 3 of 6 patients were ABC subtype. We need more patients to analyse the impact of ABC subtype in primary colorectal lymphoma survival.

Survival rate is poor, as we have reported. Unspecific symptoms make this entity difficult to diagnose and, in the majority of cases, the disease is advanced at the time of the first treatment. Histological grade and need of emergency surgery seem to be factors affecting survival (1,24).

Unfortunately, there are no controlled trials providing evidences for the optimal therapeutic approach in patients with primary colorectal lymphoma.

In conclusion, primary lymphoma of the colon and rectum is a rare tumor. Combination of chemotherapy and surgery seems to be the most effective treatment in the majority of patients. Nevertheless, the optimal management of primary lymphoma of the colon and rectum is not established. The new immunochemotherapies may have an impact on primary colorectal lymphoma survival. Moreover, identification of different subtypes of gene expression profiles could lead to improve treatment options.

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