Primary colonic lymphoma: report of two cases and a literature review

Li Chen¹,*, Qing Sun²,*, Engeng Chen¹, Dongai Jin¹ and Zhangfa Song¹

Abstract
Primary colonic lymphoma is a very rare malignant tumor with no standard treatment. We report two cases of primary colonic lymphoma successfully treated with surgery and chemotherapy, and chemotherapy alone, respectively. The first case was a 61-year-old woman who presented with abdominal pain of more than 1 month. The patient was diagnosed with a colonic tumor, and immunohistochemical examinations confirmed the initial diagnosis of colonic lymphoma. The patient underwent laparoscopic-assisted right hemicolectomy followed by postoperative adjuvant chemotherapy with the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen, combined with targeted therapy with rituximab (R-CHOP). The second case was a 78-year-old man who presented with a complaint of abdominal distention for more than 1 year. Diffuse large B-cell lymphoma was definitively diagnosed by immunohistochemical examinations, and the patient underwent systemic chemotherapy with the R-CHOP regimen. Primary colonic lymphoma is a rare type of non-Hodgkin’s lymphoma (NHL), and the clinical treatment is not standardized, unlike for many other types of lymphoma. Therefore, treatment is mainly based on the patient’s symptoms to determine whether surgery or systemic chemotherapy is appropriate. Rituximab is effective in some patients and may play an important role in the treatment of unresectable or asymptomatic colonic lymphoma.

Keywords
Case report, lymphoma, colon, chemotherapy, rituximab, non-Hodgkin’s lymphoma

Date received: 3 January 2021; accepted: 22 April 2021

¹Department of Colorectal Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China
²Department of Colorectal Surgery, Zhuji People’s Hospital of Zhejiang Province, China

*These authors contributed equally to this work.

Corresponding author:
Zhangfa Song, Department of Colorectal Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, No. 3 Qingchun East Road, Hangzhou 310000, China.
Email: songzhangfa@zju.edu.cn
Introduction

Primary colonic lymphoma is a rare malignant disease, although the gastrointestinal tract is the main site of extranodal non-Hodgkin's lymphoma (NHL). B-cell lymphoma is the third most common colorectal malignancy after colorectal cancer and neuroendocrine tumors, with an incidence of <0.5%. Elderly patients account for the majority, according to previous statistics, but the etiology and standardized treatment are not well established. We report two cases of primary lymphoma of the colon successfully treated with surgery and chemotherapy, and chemotherapy alone, respectively.

Case presentation

Case 1

A 61-year-old Chinese woman was admitted to the Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China on 22 September 2017 with a history of abdominal pain for more than 1 month. There was no fever and no change in stool characteristics and stool habits. Except for the presence of pallor, the general physical examination findings were normal. The results of routine laboratory investigations were within normal limits except for a hemoglobin concentration of 89 g/L, and a lactate dehydrogenase concentration that was higher than the normal limit. Colonoscopy showed an ascending colonic mass with partial luminal obliteration (Figure 1a). Contrast-enhanced computed tomography (CT) revealed a malignant mass (4.9 cm × 3.8 cm) in the ascending colon with peripheral lymph node metastasis extending through the serosal layer (Figure 2). Tumor marker concentrations, namely cancer antigen (CA)-125, CA19-9, and carcinoembryonic antigen, were within normal limits. After the initial pathological examination, the mass was considered to be lymphoma. Immunohistochemically, tumor cells were positive for cluster of differentiation (CD) 20, CD10, and B-cell lymphoma-6 (BCL-6), but negative for CD3 and multiple myeloma oncogene-1 (MUM-1); the Ki-67 index was 80% (Figure 3a–d). Finally, the clinical impression and results of the immunohistochemical examination established a final diagnosis of diffuse large B-cell lymphoma (DLBCL). Considering that the patient had abdominal pain and incomplete intestinal obstruction, she underwent laparoscopic-assisted right hemicolectomy on 26 September 2017. The operation was successful, and she recovered well postoperatively. Postoperative pathological examination confirmed the diagnosis of diffuse large B-cell lymphoma.

Postoperatively, the patient was transferred to the Department of Hematology, and positron emission tomography (PET)-CT revealed enlarged cervical lymph nodes. The diagnosis was confirmed as DLBCL, germinal center-like B cell (GCB) type, stage IIIA; the international prognostic index (IPI) score was 4. After excluding chemotherapy contraindications, six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy were performed from November 2017 to March 2018. No tumor recurrence was seen during the 3-year follow-up.

Case 2

A 78-year-old Chinese man was admitted to the Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China on 15 June 2018 with a complaint of abdominal distention and pain for more than 1 year. There was no nausea and vomiting, no anal exhaust, no fever, and no bloody stool or other
symptoms. The results of laboratory evaluations were normal except for a hemoglobin concentration of only 77 g/L. Contrast-enhanced CT revealed that the transverse colonic wall was thickened, the lumen was not narrow, and multiple enlarged lymph nodes were found near the serosal layer (Figure 4). Colonoscopy showed irregular hyperplasia, congestion and crispness of the intestinal mucosa in the mid-transverse colon (Figure 1b). After multipoint biopsy and pathological analysis, a malignant tumor was considered. Immunohistochemically, tumor cells were positive for CD20 and BCL-6, but negative for CD3 and CD10; the Ki-67 index was 90%. Finally, we definitively diagnosed DLBCL. As the patient had no obvious intestinal symptoms, he was transferred to the Department of Hematology. After excluding chemotherapy contraindications, six cycles of reduced-dose R-CHOP chemotherapy were performed from July 2018 to November 2018. The patient was recently followed-up, and CT and colonoscopy showed no recurrence.

Discussion

NHLs are a group of malignancies that originate from B-cell precursors, T-cell precursors, mature B-cells, mature T-cells, or natural killer cells (in a few cases). Aggressive lymphomas usually present acutely or subacutely, with manifestations of a rapidly growing mass, systemic B-cell-related symptoms (i.e., fever, night sweats, weight loss), and/or elevated serum lactate dehydrogenase and uric acid concentrations. Aggressive lymphomas include diffuse large B-cell lymphoma, Burkitt’s lymphoma, adult T-cell leukemia/lymphoma, and precursor B- and T-cell
lymphoblastic leukemia/lymphoma. \cite{1-5}

Indolent lymphomas are usually more occult, with manifestations of slowly progressive lymphadenopathy, hepatomegaly, splenomegaly, or pancytopenia, and mainly include follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and splenic marginal zone lymphoma. \cite{4-6}

Gastrointestinal lymphomas account for 5\% to 10\% of all NHLs, most of which occur in the stomach (accounting for 68\%–75\% of all gastrointestinal lymphomas), followed by the small intestine (15\%–20\%), with the remainder occurring in the colon, rectum and esophagus. \cite{1-4} The gastrointestinal tract is the main site of extranodal NHL. Lymphoma can involve a single primary site and can also affect multiple gastrointestinal sites, and local and distant lymph nodes can also be involved. Primary gastrointestinal NHL is rare, accounting for only 1\% to 4\% of

Figure 3. Histological features and immunohistochemical results of colonic lymphoma. (a) Morphological examination (hematoxylin and eosin staining; magnification, \times100); (b) Morphological examination (hematoxylin and eosin staining; magnification, \times200). Tumor cells demonstrate marked positivity for (c) CD10 and (d) CD20 (immunostaining; magnification, \times200).

CD, cluster of differentiation.

Figure 4. Abdominal contrast-enhanced computed tomography (CT) (horizontal view) showing a thickened colonic wall (red stars).
malignancies originating from the stomach, small intestine, or colon. B-cell lymphoma is the third most common colorectal malignancy after colorectal cancer and neuroendocrine tumors, with an incidence of <0.5%. DLBCL is the most common histological subtype of gastrointestinal lymphoma, and is more aggressive than other B-cell lymphomas. The final pathological results in both of our patients was DLBCL. The pathogenesis of gastrointestinal lymphomas is associated with a variety of factors, and no specific risk factors have been identified. Helicobacter pylori infection is closely associated with the development of gastric mucosa-associated lymphoid tissue (MALT) lymphoma and is also related to other gastrointestinal lymphomas with a slightly lower degree of association. Many autoimmune diseases are associated with an increased risk of lymphoma, namely rheumatoid arthritis, Sjogren’s syndrome, systemic lupus erythematosus, and granulomatosis with polyangiitis, which may be because of the increased cancer risk with immunosuppressive therapy. Colorectal B-cell lymphoma has a variety of clinical manifestations, and its symptoms depend on the lesion location. In the colon, the incidence of right colonic B-cell lymphoma is higher than in other parts of the colon. Our two cases of lymphoma were located in the ascending colon and transverse colon, respectively. The most common symptoms are abdominal pain, weight loss, abdominal mass, and blood in the stool, as well as nausea, vomiting, altered bowel habits, obstruction, and acute peritonitis owing to intussusception and intestinal perforation. Fan et al. found that abdominal pain and weight loss occurred in 62% and 43% of 37 patients, respectively, while Bairey et al. reported that abdominal pain and weight loss occurred in 56% and 29% of patients, respectively. Complete intestinal obstruction is a very rare clinical manifestation because colorectal lymphoma is more malleable than adenocarcinoma and does not promote connective tissue hyperplasia; however, incomplete intestinal obstruction is more common. Similarly, the main symptoms were abdominal pain and anemia in our two cases. Surprisingly, in most of the colorectal B-cell lymphoma cases reported in the literature, B-cell-related symptoms were not usually present, and fever was a rare symptom, possibly because of the initial presence of intestine-related symptoms. The most common imaging examination for colorectal lymphomas is contrast-enhanced abdominal CT, which mainly provides information about tumor size, invasion depth, and local lymph node metastasis. Notably, CT cannot distinguish adenocarcinoma and lymphoma very well, and the diagnosis must be confirmed by colonoscopic biopsy. Colonoscopic findings can include diffuse mucosal nodules, colitis-like changes associated with induration and ulcers, or masses with or without ulcers. Multipoint biopsy should be performed for all lesions using standard methods, and tumor classification requires immunohistochemistry. Comprehensive examinations, including peripheral blood tests, biochemical tests, chest and abdominal CT, and bone marrow biopsy, are needed to exclude systemic involvement and identify disease stage. Both of our patients were diagnosed by multipoint biopsy combined with immunohistochemistry. The most widely used clinical staging system is the Lugano classification, a modification of the Ann Arbor classification. The main treatment for colorectal lymphoma is combined therapy with surgery and chemotherapy. Early-stage tumors are mainly treated with surgery combined with postoperative chemotherapy, and advanced tumors are treated with multidrug
chemotherapy (CHOP protocol).\textsuperscript{20,21} However, owing to the effectiveness of recent targeted drugs, especially rituximab, CD20-positive B-cell lymphoma can be treated with multidrug chemotherapy combined with immunotherapy, and the treatment efficacy is long-lasting and complete.\textsuperscript{22,23} According to previous case reports, immunotherapy can obviate surgery, which is mainly performed to relieve pain and for emergencies, such as intestinal obstruction, intestinal perforation, and hemorrhage.\textsuperscript{24,25} The best treatment for rapidly proliferating and aggressive advanced colorectal lymphoma is chemotherapy. The CHOP chemotherapy regimen is the primary treatment for intermediate-stage and advanced B-cell lymphomas. Adding rituximab to the standard CHOP regimen may improve the progression-free- and overall survival rates.\textsuperscript{20–23} If the treatment response is incomplete or the probability of recurrence is high, bone marrow transplantation or stem cell transplantation is performed. Because the disease is rare, current guidelines still lack high-level evidence for selecting the best treatment for gastrointestinal lymphomas.

Although treatment has improved, primary colorectal lymphoma, especially DLBCL, is still an invasive disease with a poor prognosis.\textsuperscript{26} Fan et al. found that tumor stage was the most important prognostic factor for survival,\textsuperscript{4} while others researchers found that histological grade is the most important prognostic factor.\textsuperscript{19} The IPI is a commonly used prognostic scoring system for NHL and is also useful for colorectal lymphoma.

In our first case, because of the obvious symptoms of abdominal pain and incomplete intestinal obstruction, we chose surgical resection and postoperative adjuvant chemotherapy. In the second case, there was no obvious discomfort; therefore, systemic chemotherapy was used; both patients were treated with the R-CHOP regimen. Fortunately, the therapy was very effective in each patient, although the treatment methods differed.

The present study aimed to increase awareness among clinicians. Primary colonic lymphoma is a rare type of NHL, and the clinical treatment is not standardized, unlike for many other types of lymphoma. The patient’s symptoms are used to determine whether surgery or systemic chemotherapy is appropriate. Rituximab is effective in some patients, which may play an important role in the treatment of unresectable or asymptomatic colonic lymphoma.\textsuperscript{27} Long-term efficacy requires longer follow-ups and large-scale future research.

Acknowledgment

Our special thanks are due to Prof. He Chao for his help in preparing the manuscript.

Authors’ contributions

Conceptualization: LC, QS, ZFS
Data curation: LC, QS, EGC
Formal analysis: LC, QS, EGC
Methodology: LC, QS, EGC
Resources: LC, QS, EGC, DAJ
Software: EGC
Writing – original draft: LC
Writing – review & editing: LC, QS, EGC, ZFS

All authors have read and approved the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics statement

This study was approved by the ethics committee of Sir Run Run Shaw Hospital, Zhejiang University College of Medicine. Written consent was obtained from the patients to publish their personal or clinical details along with any identifying images.
Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Zhejiang University College of Medicine.

ORCID iD
Zhangfa Song https://orcid.org/0000-0001-6301-1813

References
1. Mouchli MA, Ouk L, Scheitel MR, et al. Colonoscopy surveillance for high risk polyps does not always prevent colorectal cancer. *World J Gastroenterol* 2018; 24: 905–916.
2. Zinzani PL, Magagnoli M, Pagliani G, et al. Primary intestinal lymphoma: clinical and therapeutic features of 32 patients. *Haematologica* 1997; 82: 305–308.
3. Tahir M, Samad K, Koenig T, et al. A rare case of primary diffuse large B-cell lymphoma of the colon. *AME Case Rep* 2018; 2: 28.
4. Fan CW, Changchien CR, Wang JY, et al. Primary colorectal lymphoma. *Dis Colon Rectum* 2000; 43: 1277–1282.
5. Shaye OS and Levine AM. Marginal zone lymphoma. *J Natl Compr Canc Netw* 2006; 4: 311–318.
6. Quayle FJ and Lowney JK. Colorectal lymphoma. *Clin Colon Rectal Surg* 2006; 19: 49–53.
7. Yoshino T, Ichimura K, Mannami T, et al. Multiple organ mucosa-associated lymphoid tissue lymphomas often involve the intestine. *Cancer* 2001; 91: 346–353.
8. Ha CS, Cho MJ, Allen PK, et al. Primary non-Hodgkin lymphoma of the small bowel. *Radiology* 1999; 211: 183–187.
9. Pandey M, Kothari KC, Wadhwa MK, et al. Primary malignant large bowel lymphoma. *Am Surg.* 2002; 68: 121–126.
10. Ferreri AJ and Montalbán C. Primary diffuse large B-cell lymphoma of the stomach. *Crit Rev Oncol Hematol* 2007; 63: 65–71.
11. Zhai L, Zhao Y, Lin L, et al. Non-Hodgkin’s lymphoma involving the ileocecal region: a single-institution analysis of 46 cases in a Chinese population. *J Clin Gastroenterol* 2012; 46: 509–514.
12. Busch E, Rodriguez-Bigas M, Mamounas E, et al. Primary colorectal non-Hodgkin’s lymphoma. *Ann Surg Oncol* 1994; 1: 222–228.
13. She WH, Day W, Lau PY, et al. Primary colorectal lymphoma: case series and literature review. *Asian J Surg* 2011; 34: 111–114.
14. Matsumoto T, Iida M and Shimizu M. Regression of mucosa-associated lymphoid tissue lymphoma of rectum after eradication of Helicobacter pylori. *Lancet* 1997; 350: 115–116.
15. Nakamura S, Yao T, Aoyagi K, et al. Helicobacter pylori and primary gastric lymphoma. A histopathologic and immunohistochemical analysis of 237 patients. *Cancer* 1997; 79: 3–11.
16. Zhou JL, Qiu HZ, Sun J, et al. [The diagnosis and treatment of colorectal Non-Hodgkin’s lymphoma 32 cases]. *Zhonghua Wai Ke Za Zhi* 2011; 49: 290–294.
17. Tevlin R, Larkin JO, Hyland JM, et al. Primary colorectal lymphoma - A single centre experience. *Surgeon* 2015; 13: 151–155.
18. Bairey O, Ruchlemer R and Shpilberg O. Non-Hodgkin’s lymphomas of the colon. *Isr Med Assoc J* 2006; 8: 832–835.
19. Li B, Shi YK, He XH, et al. Primary non-Hodgkin lymphomas in the small and large intestine: clinicopathological characteristics and management of 40 patients. *Int J Hematol* 2008; 87: 375–381.
20. Pfreundschuh M, Trümper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MiNt) Group. *Lancet Oncol* 2006; 7: 379–391.
21. Hammel P, Haioun C, Chaumette MT, et al. Efficacy of single-agent chemotherapy in low-grade B-cell mucosa-associated lymphoid tissue lymphoma with prominent gastric expression. *J Clin Oncol* 1995; 13: 2524–2549.
22. Salar A, Domingo-Domenech E, Estany C, et al. Combination therapy with rituximab and intravenous or oral fludarabine in the first-line, systemic treatment of patients with extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type. Cancer 2009; 115: 5210–5217.

23. Raderer M, Jäger G, Brugger S, et al. Rituximab for treatment of advanced extranodal marginal zone B cell lymphoma of the mucosa-associated lymphoid tissue lymphoma. Oncology 2003; 65: 306–310.

24. Koniaris LG, Drugas G, Katzman PJ, et al. Management of gastrointestinal lymphoma. J Am Coll Surg 2003; 197: 127–141.

25. Cai S, Cannizzo F Jr, Bullard Dunn KM, et al. The role of surgical intervention in non-Hodgkin’s lymphoma of the colon and rectum. Am J Surg 2007; 193: 409–412; discussion 412.

26. Freeman C, Berg JW and Cutler SJ. Occurrence and prognosis of extranodal lymphomas. Cancer 1972; 29: 252–260.

27. Morrison VA. Evolution of R-CHOP therapy for older patients with diffuse large B-cell lymphoma. Expert Rev Anticancer Ther 2008; 8: 1651–1658.