Colorectal Lymphoma

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ABSTRACT

Lymphoma involving the colon and rectum is rare and can occur either as primary colorectal lymphoma or as a manifestation of systemic disease. Most patients with primary colorectal lymphoma present with abdominal pain, and obstruction is unusual. Although lesions may be evident on radiographic studies, the findings are generally nonspecific. Historically, aggressive B-cell lymphomas have been the most common gastrointestinal lymphomas reported in the literature. However, recent reports suggest increased rates of mucosa-associated lymphoid tissue (MALT) lymphoma and mantle cell lymphoma (MCL) with increased surveillance. Most patients with colorectal lymphoma undergo surgery, but multiagent chemotherapy remains the mainstay of treatment. B-cell lymphomas tend to be most aggressive, with a median survival of about 2 years.

KEYWORDS: Lymphoma, immunosuppression

Objectives: Upon completion of this article, the reader should be familiar with methods of diagnosis and treatment of colorectal lymphomas.

Lymphomas are hematologic malignancies with a wide variety of histologic subtypes and a broad spectrum of clinical behavior, aggressiveness, and prognosis. Despite the existence of effective therapy, lymphoma is the sixth most common cause of cancer death in the United States with an incidence that has been increasing in recent decades.¹ Approximately 40% of lymphomas have extranodal manifestations, and the most common site of extranodal involvement is the gastrointestinal tract.² Nonetheless, colorectal lymphoma remains a rare clinical entity. The aim of this article is to provide an overview of colorectal lymphoma with emphasis on clinical presentation, histologic subtypes, management, and prognosis.

Although the gastrointestinal tract is the most common site of extranodal lymphoma, colorectal lymphoma is rare. Colorectal lymphomas account for only 15 to 20% of gastrointestinal lymphomas, a lower rate of

involvement than either stomach (50 to 60%) or small intestine (20 to 30%).³ Colorectal lymphoma differs from its gastric counterpart not only in pathology but also in its presentation, treatment, and prognosis. Overall, primary colorectal lymphoma accounts for 1.4% of all cases of non-Hodgkin's lymphoma (NHL)⁴ and less than 1% of all colorectal malignancies.⁵

Primary gastrointestinal lymphoma is a disease entity that occurs in the absence of evidence of systemic disease. The original criteria for primary gastrointestinal lymphoma, described by Dawson et al in 1961, included (1) the absence of clinically enlarged lymph nodes on physical examination, (2) the absence of enlarged mediastinal lymph nodes on chest radiograph, (3) normal hematologic laboratory values and bone marrow biopsy, and (4) normal-appearing liver and spleen, all in the setting of lymphoma occurring in a portion of the

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gastrointestinal tract.⁶ These criteria have been expanded in the current era of computed tomography with the requirement that retroperitoneal or mediastinal lymphadenopathy be excluded.

HISTOLOGIC SUBTYPES AND STAGING

Many classification schemes have been described to categorize NHLs, reflecting wide variability in histologic appearances, clinical behavior, and responses to therapy for different lymphoma subtypes (see Table 1). The World Health Organization (WHO) classification subtypes lymphomas into diffuse large B-cell lymphoma, extranodal marginal zone lymphoma (mucosa-associated lymphoid tissue [MALT]-associated lymphoma), mantle cell lymphoma (MCL), Burkitt's lymphoma, and follicular lymphoma.⁷

The most common histologic subtype affecting the gastrointestinal tract and colon is diffuse large B-cell lymphoma.^{3,8} These are generally aggressive and are composed of rapidly proliferating cells of B-cell origin. The second most common colorectal lymphoma is MALT-associated low-grade B-cell lymphoma. MALT-associated lymphomas are low-grade tumors arising from B cells associated with mucosal immunity. MALT-associated lymphomas are most commonly seen in the stomach, where they are often preceded by a chronic inflammatory state, such as *Helicobacter pylori* infection. Gastric MALT-associated lymphomas can be successfully treated by *H. pylori* eradication alone.⁸ Colorectal MALT-associated lymphomas do not have the same association with *H. pylori* infection and, therefore, behave and are treated as a different clinical entity. MCLs are diffuse, small cleaved cell lymphomas with a significant male predominance and a generally poor prognosis.⁹ Recent reports suggest that MCLs often involve the colon and rectum, although mostly in the setting of diffuse systemic disease.¹⁰ T-cell lymphoma and Hodgkin's lymphoma affecting the colon have been described but are rare.¹¹

Lymphomas are generally staged according to the number and sites of nodal and extranodal involvement, and multiple staging schemes have been described. The Ann Arbor staging system modified by Musshoff is widely used in clinical practice today¹² (see Table 2). Most colorectal lymphomas that undergo surgical intervention are stage IE or IIE, disease confined to the colon or rectum without (IE) or with (IIE) regional lymph node involvement.

PRESENTATION/RADIOGRAPHIC FINDINGS

Primary colorectal lymphoma has an increasing incidence with age and most often affects patients in the fifth to seventh decades of life. Affected men outnumber

women about 1.5:1.^{5,8} These demographic patterns mirror those of NHL in general. As with other types of lymphoma, patients with chronic immunosuppression including patients with inflammatory bowel disease, those with human immunodeficiency virus infection, and transplant recipients are at increased risk for colorectal lymphoma.

The most common presenting symptoms in patients with primary colorectal lymphoma are weight loss and abdominal pain. Fan et al reported that 62% of patients presented with pain and 43% presented with weight loss in their series of 37 patients with colorectal lymphoma,⁵ and Zigelboim and Larson reported a 40% rate of abdominal pain and weight loss in their series of 15 patients with colorectal lymphoma.⁸ Lower gastrointestinal bleeding occurs in approximately 20% of patients.^{5,8}

Up to half of patients present with a palpable abdominal mass, suggesting that these tumors can be present for a long period of time without causing symptoms. Conversely, obstruction is a rare event and occurs much less often in patients with colorectal lymphoma than those with colorectal adenocarcinoma. This is probably due to the more pliable nature of colorectal lymphomas and the absence of a desmoplastic response. In addition, patients with colorectal lymphoma rarely present with bowel perforation.

The majority of colorectal lymphomas are found in the cecum or ascending colon. More than 70% of colorectal lymphomas are proximal to the hepatic flexure. Indeed, some series of gastrointestinal lymphomas distinguish ileocecal lymphoma as an entity distinct from both small intestinal lymphomas and colonic lymphomas.³ Tumors of the descending and rectosigmoid colon account for about 25% of colorectal lymphomas.^{5,13}

Colorectal lymphoma is most often imaged using computed tomography (CT) or double-contrast barium enema; these modalities are complementary to each other. CT scans can give extraluminal, anatomic information regarding tumor size, depth of invasion, and regional lymph node involvement. Double-contrast enema offers superior examination of subtle mucosal changes as well as gross tumor morphology. Positron emission tomography (PET) may also aid in the diagnosis and follow-up of patients with lymphomas, although its role has not been determined.¹⁴

Radiographic findings associated with colorectal lymphoma can be localized or diffuse. The spectrum of findings includes a polypoid mass, circumferential or cavitory lesions, focal mucosal nodularity, and diffuse ulcerative or nodular lesions (the latter is known as lymphomatous polyposis). Most often colorectal lymphomas are large, polypoid lesions and mucosal ulceration is unusual. The radiographic findings associated with colorectal lymphoma are generally nonspecific and have significant overlap with those in other types of

Table 1 Classifications Categorizing NHLs

WHO	REAL	Working	Lukes-Collins	Kiel	Rappaport
Extranodal marginal zone lymphoma (MALT lymphoma)		Small lymphocytic, lymphoplasmacytoid	Small cleaved cell type	Immunocytoma	Well-differentiated lymphocytic
Follicular lymphoma	Follicular center lymphoma	Follicular small cleaved	Small cleaved cell type	Centroblastic/centrocytic, follicular and diffuse	Nodular poorly differentiated lymphocytic
Mantle cell lymphoma		Small cleaved cell type		Centrocytic	Intermediately or poorly differentiated lymphocytic
Diffuse large B-cell lymphoma	Diffuse large B-cell lymphoma	Large cell immunoblastic	Large cleaved follicular center cell	Centroblastic, B-immunoblastic	Diffuse mixed lymphocytic and histiocytic
Burkitt's lymphoma	Burkitt's lymphoma	Small noncleaved cell, Burkitt's type	Small noncleaved follicular center cell	Burkitt's lymphoma with intracytoplasmic immunoglobulin	Undifferentiated lymphoma, Burkitt's-type

Data from Koniaris LG, Drugas G, Katzman PJ, Salloum R. Management of gastrointestinal lymphoma. J Am Coll Surg 2003;197:127–141.

Table 2 Ann Arbor Staging System

Stage	Description
I	Involvement of a single nodal group or single extranodal site (IE).
II	Involvement of more than one nodal group on the same side of the diaphragm or single extranodal site and adjacent lymph nodes (IIE).
III	Involvement of multiple nodal sites on both sides of the diaphragm, including extranodal sites (IIIE) or spleen (IIIS).
IV	Bone marrow, central nervous system, or diffuse visceral involvement.

Data from Carbone et al.¹²

colorectal disease. Colorectal lymphomas can share radiographic similarities with colorectal adenocarcinomas. Occasionally, the radiographic findings of colorectal lymphoma can mimic those of inflammatory bowel disease. Lymphomatous polyposis can appear radiographically similar to familial adenomatous polyposis or other clinical polyposis entities.

Owing to its rarity and nonspecific clinical and radiographic signs, the diagnosis of colorectal lymphoma requires a high index of suspicion. In a nonurgent setting, the diagnosis can generally be made preoperatively using colonoscopy to obtain tissue biopsies.

MANAGEMENT

Lymphomas were among the first tumors treated with cytotoxic chemotherapy, and today chemotherapy remains the primary therapeutic modality for most lymphomas. CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone) was a pioneering development that for the first time offered curative therapy to some patients with lymphoma.¹⁵ Even today, CHOP remains a mainstay of treatment for lymphoma.

An important feature of lymphomas is their variable susceptibility to chemotherapy regimens. Generally, rapidly proliferating tumors are more susceptible to cytotoxic chemotherapy than indolent tumors. Despite the central role of systemic chemotherapy, local therapy is often indicated because of their variable susceptibility to chemotherapy and improved outcomes associated with adjuvant regional therapy.

External beam radiation is most commonly used for regional adjuvant therapy to obtain local control in lymphoma and is considered the standard of care by many authors.¹⁶⁻¹⁹ Nonetheless, radiation therapy has certain limitations with regard to complications associated with therapy and limited control of bulky disease. The small and large intestines are particularly susceptible to complications of radiation therapy, and therefore external beam radiation is not a preferred adjuvant option in the treatment of colorectal lymphoma.

In the absence of disseminated disease, surgical resection is generally performed for colorectal lymphomas. Resection serves as therapy for local control in patients with aggressive lymphomas (diffuse B cell) whose definitive therapy will be CHOP or other polychemotherapies. Low-grade lymphomas such as MALT-associated lymphomas may have chemotherapy resistance, and surgery may serve as definitive therapy in these cases.

Almost all patients with colorectal lymphoma reported in the literature underwent some form of surgical resection.^{4,5,8,13,20} Based on these series, the proportion of patients with no regional lymph node involvement (stage IE) ranged from 14 to 24%. The majority of patients had regional lymph node involvement (stage IIE) in addition to their primary tumor at the time of surgery, ranging from 62 to 86%. These findings emphasize the importance of performing a regional lymphadenectomy with the surgical resection. A small number of patients were ultimately found to have diffuse visceral involvement at the time of laparotomy (stage IVE).

The median survival in these series is generally low, ranging from 24 to 36 months.^{5,8} In most series, the majority of patients undergo CHOP or other multiagent systemic chemotherapy following surgical resection, and systemic chemotherapy has been associated with improved outcomes. Zigelboim and Larson reported an improvement in median survival from 36 to 53 months in patients who underwent adjuvant chemotherapy.⁸ Fan et al reported improved median survival from 24 to 36 months.⁵ In their series of 53 patients with stage IE colorectal lymphoma who underwent surgical resection followed by chemotherapy, Aviles et al described an overall survival of 83% at 10 years.²⁰ Incidentally, prior to instituting routine adjuvant therapy for patients with stage IE colorectal lymphoma, Aviles et al noted a 74% rate of relapse with local or disseminated disease in stage IE patients treated with surgery alone. These results suggest that aggressively treated stage IE colorectal lymphoma is perhaps a more benign clinical entity than that which involves regional lymph nodes. They also emphasized the importance of systemic chemotherapy in the treatment of colorectal lymphoma. In fact, in most series reported in the literature, patients who underwent CHOP or other chemotherapy after surgery did better than patients who underwent surgery alone.

Unfortunately, the majority of patients with primary colorectal lymphoma ultimately have recurrences and die from their disease. Recurrence rates range from 33 to 75%, and recurrences can occur early or late. Most recurrence events occur within the first 5 years after resection. Generally, patients have recurrences with diffuse disease. These patients can be managed with salvage chemotherapy, but most ultimately die from disseminated lymphoma.

CONCLUSION

Colorectal lymphoma is a rare disease, accounting for a small proportion of both colorectal malignancies and gastrointestinal lymphoma. Most patients present with nonspecific symptoms, which often leads to delays in diagnosis and advanced stage at presentation. The majority of patients have diffuse large B-cell lymphoma. The treatment of colorectal lymphoma generally consists of surgery followed by multiagent systemic chemotherapy. Improved disease-free and overall survival rates in patients treated with chemotherapy emphasize the importance of systemic therapy in this disease. Unfortunately, despite aggressive therapy, a majority of patients with colorectal lymphoma ultimately have recurrences and go on to die from their disease.

DISCLAIMER

The authors of this article and their spouses have no financial interest in the topics discussed in this article.

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