Colorectal Lymphoma

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ABSTRACT

Extranodal lymphomas account for a third of all cases of non-Hodgkin lymphoma with the gastrointestinal tract being the most common extranodal site. The most common location is the stomach followed by the small intestine, colon and rectum. Colorectal lymphomas are rare and comprise 10–20% of all gastrointestinal lymphomas and only 1% of all colorectal malignancies. Presenting symptoms include abdominal pain, weight loss, and anorexia. Diagnosis depends on the clinical setting with elective cases being diagnosed with colonoscopy and emergent cases being diagnosed in the operating room. Colonic lymphomas are frequently located proximal to the hepatic flexure. Management depends on the aggressiveness of the lymphoma subtype. Indolent tumors, which are resistant to standard chemotherapeutic regimens, are treated with surgical resection. Aggressive lymphoma subtypes are managed with chemotherapy and surgery with late-stage disease patients being referred to clinical trials.

KEYWORDS: Lymphoma, non-Hodgkin lymphoma, gastrointestinal, intestinal tumors

Objectives: After reading this article, the readers will be familiar with the diagnosis and management of colorectal lymphomas.

Non-Hodgkin lymphomas (NHL) are a group of lymphoproliferative disorders originating from B, T, and natural killer lymphocytes. In 2010, 65,540 new cases of NHL will have been diagnosed and slightly more than 20,000 individuals will have died of the disease. NHL incidence has been stable for men since 1991, but increasing by 1.1% per year for women since 1990. The disease remains more common in men. It is usually a disease of the elderly with men over the age of 70 having a 1 in 58 chance of developing the disease compared with men under age 40 who have a 1 in 782 chance. Survival is dependent on histology and stage with a 5-year survival rate of 67%.¹

Extranodal lymphomas are lymphomas originating in solid organs. Extranodal lymphomas accounted for 34% of all cases of non-Hodgkin lymphoma in a large population-based study in the Netherlands.² The gastro-

intestinal (GI) tract is the most common location for extranodal lymphoma. Within the GI tract, the most common sites are the stomach, small intestine, and colon/rectum.^{3,4} Colorectal lymphomas account for only 10–20% of GI lymphomas, whereas the stomach and small bowel comprise 40–50% and 20–30% respectively.^{5,6} Colorectal lymphomas are a rare diagnosis accounting for only 0.9 to 1.2% of all colorectal malignancies.⁷

Primary GI lymphomas were defined by Dawson et al in 1961.⁸ There are five components: (1) no palpable, superficial lymph nodes at presentation; (2) no enlarged mediastinal lymph nodes on chest x-ray; (3) normal range for white blood cell count including total and differential; (4) at surgery, only the regional lymph nodes are involved; and (5) the liver and spleen are without disease. There are 11 retrospective reviews in the medical literature that follow strict Dawson

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Table 1 Musshoff Modifications to Ann Arbor Staging System for Extranodal Lymphoma^{25,27}

Stage I or Stage IE	Single lymphatic organ or extranodal site
Stage II	Two or more lymphatic regions on the same site of the diagram or a single extranodal organ and lymph node involvement at the same site of diaphragm
Stage II ₁	Regional lymph nodes involved
Stage II ₂	Distant lymph nodes involved
Stage III	Lymph nodes involved on both sides of diaphragm
Stage IV	Disseminated disease with involvement of bone marrow, liver, etc.

criteria.⁹⁻¹⁹ The number of subjects in each study varies from 7 to 95. Population-based studies of GI lymphoma were larger varying in size from 55 to 1069 with colorectal lymphoma cases falling between 9 and 71.^{5,6,20-24}

STAGING AND CLASSIFICATION

Staging and classification of non-Hodgkin lymphoma is critical for standardizing diagnosis, medical and surgical treatment, and management. The Ann Arbor staging system, which was initially created for Hodgkin lymphoma, has been adapted by most physicians. For staging of primary GI lymphoma, modifications to the Ann Arbor system have been proposed. The modifications by Musshoff are frequently cited because they break down positive lymph node status into regional, noncontiguous regional and distant lymph node locations.²⁵ When compared with the Ann Arbor staging system, the Musshoff modified system was more informative in predicting overall and disease-free survival for locally advanced and regional disease²⁶ (Table 1).²⁷ In addition, it easily discriminates between localized and widely disseminated disease.²²

Non-Hodgkin lymphomas can arise from B cells, T cells, and natural killer cells. Every level of lymphoid development can be associated with malignancy. After the cell of origin is identified, tumor cells are determined to be from precursor or mature lymphocytes.²⁸ The tremendous variation in subtype leads to differences in growth, dissemination, response to therapy, and outcomes.²⁹ Therefore, classification and the ability to identify subtypes are essential for management. There are multiple classification systems: World Health Organization (WHO), Kiel, Rappaport, Luke-Collins, and Revised European American Lymphoma (REAL) (Table 2).²⁹

The WHO criteria divide GI lymphomas into diffuse large cell, extranodal marginal zone lymphoma (mucosa-associated lymphoid tissue [MALT]), Burkitt, peripheral T cell, mantle cell, and follicular cell.³⁰ There are more than 50 types and subtypes listed, which are identified by specific histologic, immunologic, genetic, and clinical characteristics.²⁸ The most common subtype in the colon is diffuse large B-cell lymphoma (60%), followed by MALT (15%) and Burkitt (15%).²⁹ Diffuse large B-cell lymphomas (DLBCL) can develop *de novo* or as a transformation from a less-aggressive type of lymphoma such as chronic lymphocytic leukemia, follicular lymphoma, or marginal zone B-cell lymphoma. DLBCL is usually positive for CD-19, CD-20, and CD79a.

MALT can be of two types. The first type affects the organs where lymph node tissue is usually present such as Peyer patches. The second type of MALT arises in the setting of a chronic inflammatory or autoimmune disorder. In this type of environment, where inflammation is present for long periods, abnormal lymphoid cells can grow rapidly, replacing the normal lymphoid tissue.³¹

Burkitt lymphoma (BL) is defined in the WHO criteria as an aggressive B-cell non-Hodgkin lymphoma with intense proliferation and deregulation of the c-MYC

Table 2 Classification Systems for Lymphoma

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

Comparison of GI Lymphoma Classifications adapted from Koniaris et al.²⁹
WHO, World Health Organization; REAL, Revised European American Lymphoma.

gene.^{30,32} BL etiologies include sporadic, endemic, and immunodeficient and can be differentiated by the patient's clinical environment.³² BL is composed of mature B-cells that are positive for CD19, CD20, CD22, and CD79a.

PRESENTATION

Information regarding presentation of colonic lymphoma is derived from retrospective reviews. Even though the population-based studies have larger sample sizes, they do not have symptoms consistently divided by site. Abdominal pain was noted in up to 77% of patients and was the most common presenting symptom.^{4,9,10} Constitutional symptoms such as weight loss or anorexia were present in 30 to 50% of patients.^{4,9,12} Blood per rectum was less common occurring in 0 to 30% of patients.^{4,9–12,14} Palpable abdominal mass was noted in three studies with the following percentages: 28.6, 54.0, and 77.1.^{4,10,12}

The most common location for colonic lymphoma is the cecum occurring in 30 to 60% of patients.^{9–13} Lesions proximal to the hepatic flexure account for 67.6 to 87% of all colonic lymphomas.^{9,11,12,33} The next most common sites are the sigmoid and rectum, which combine for 10 to 25% of colonic lymphomas.^{9–12,14}

DIAGNOSIS AND IMAGING

In an elective setting, the diagnosis of colonic lymphoma can be made with colonoscopy. Colonoscopic findings include a polypoid or ulcerated mass, intramural lesion, aphthous ulcer, stricture, extraluminal mass, or diffuse,

multiple polypoid lesions.³⁴ Myung et al classified ileocolonic lymphomas based on their colonoscopic appearance: fungating, ulcerofungating, infiltrative, ulceroinfiltrative, and ulcerative.³⁵

Computed tomography (CT) and barium enema (BE) are the two radiographic procedures used to diagnose and evaluate colonic lymphoma. CT is beneficial for diagnosing the extent of colonic wall thickening, regional lymph node involvement, and distant disease. BE provides assessment of the mucosa and morphology of the mass.³⁶ Hyun et al have described the following imaging findings for colonic lymphoma (Table 3).³⁶ Lesions are either focal or diffuse. Focal lesions can be polypoid, circumferential with smooth mucosal surface, circumferential with extensive ulceration, a cavitary mass, a mucosal fold thickening, and a focal mucosal nodularity. Diffuse lesions are described as ulcerated or nodular.

Despite the long segment and circumferential involvement, lymphomas do not have a desmoplastic reaction and rarely cause obstruction.³⁷ The long, annular lesions help distinguish lymphoma from the short, apple core lesions of adenocarcinoma. In addition, extension into the terminal ileum, lack of invasion into nearby structures, and preservation of the fat planes are findings that differentiate lymphoma from adenocarcinoma.³⁸ In rectal lymphoma, almost any presentation is possible ranging from lesions that are indistinguishable from adenocarcinoma to long segment involvement and aneurysmal dilatation.^{38,39}

Unfortunately, colonic lymphomas can present as surgical emergencies. In Wong's study, 9 of 14 patients with colonic lymphoma required emergent surgery.¹⁰ In

Table 3 Radiographic Characteristics of Colonic Lymphoma³⁶

	Focal Lesion	Diffuse Lesion
Polypoid mass	2–20 mm in size, frequently located near ileocecal valve with extension into ileum. Polypoid colorectal lymphomas are larger than adenocarcinoma and can extend through the bowel wall into the peritoneum	
Circumferential, smooth mucosal surface	Long segment of colon with concentric narrowing, mucosa is smooth, abnormal haustral folds	
Circumferential, extensive ulceration	Infiltrative with mucosal ulceration	
Cavitary mass	Invasion into the mesentery produces a cavitary lesion that appears as a contrast-filled cavity on the mesenteric border	
Mucosal fold thickening	Caused by submucosal infiltration of lymphoid cells	
Focal mucosal nodularity	Mucosal nodularity in a short length of colon, unusual	
Ulcerative		Diffuse, ulcerative mucosa. Difficult to distinguish from IBD
Nodular		Multiple, small sessile nodules in a long segment of colon or throughout the colon

IBD, inflammatory bowel disease.

these settings, the information obtained from CT imaging, operative findings, and pathology will make the diagnosis.

The role of positron emission tomography (PET) in the diagnosis and management of non-Hodgkin lymphoma has not been standardized. Currently studies are evaluating PET after completion of treatment and to assess interim response to chemotherapy. Two studies have shown that PET identifies residual lymphoma after treatment better than CT.^{40,41} A meta-analysis evaluating PET for interim response showed significant heterogeneity in clinical management, therapy, and timing of PET scans.^{42,43} Multi-centered, randomized studies evaluating the use of PET for interim assessment, prognosis, end of treatment results, and follow-up need to be performed before the role of PET in the management of non-Hodgkin lymphoma can be standardized.

MANAGEMENT

Treatment of colonic non-Hodgkin lymphoma is multimodal. Certain indolent lymphomas are resistant to the standard chemotherapeutic regimen CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). The variability of lymphomas to respond to chemotherapy allows surgical resection to play a more dominant role in early-stage disease. For localized disease, stage I or II, surgery with removal of all gross disease should be performed. For disseminated disease, the surgical plan includes obtaining tissue for diagnosis, repair/resection of perforated viscus, and enteric bypass.²⁹ The overall 5-year mortality rate ranges from 33 to 58%.^{12,44,45}

Approach to Aggressive Lymphomas

Aggressive lymphomas include diffuse large B cell and mantle cell. Highly aggressive lymphomas are Burkitt lymphoma, lymphoblastic lymphoma, and acquired immune deficiency syndrome (AIDS)-related B-cell lymphoma.⁴⁷ For diffuse large B-cell lymphoma, the workup includes physical exam, performance status, B symptoms, complete blood count (CBC) with differential, metabolic panel, lactate dehydrogenase (LDH), uric acid, CT chest/abdomen/pelvis, hepatitis B, and CT PET.⁴⁶ Patients with stage I and II disease are treated with surgery and chemotherapy. The chemotherapy regimen is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Patients with stage III or IV disease are referred to a clinical trial.⁴⁶ For patients with Burkitt lymphoma, the workup is similar, but also includes lumbar puncture, flow cytometry of cerebrospinal fluid, and bone marrow biopsies. Patients with resected abdominal lesions and normal LDH are considered low risk and are referred to

a clinical trial or treated with cyclophosphamide-based chemotherapy.⁴⁶

Approach to Indolent Lymphomas

Indolent lymphomas include follicular and MALT. For follicular and nongastric MALT lymphomas, the workup includes a physical exam with performance status, B symptoms, CBC with differential, metabolic panel, LDH, hepatitis B testing if rituximab may be used, and CT chest/abdomen/pelvis. If disease is stage I or II, surgery is recommended. If the margins are negative, the patient can be observed. If margins are positive then consider localized radiotherapy.⁴⁶ For patients with stage III or IV disease, surgery is not for cure and is used to ameliorate complications of the disease. For patients who meet the indications for treatment (progression, candidate for clinical trial, bulky disease, end-organ threatened, personal preference, or cytopenia) options include chemotherapy that is rituximab-based, radiation therapy, or a clinical trial.⁴⁶ The 5-year survival rate in a study evaluating GI follicular lymphoma in patients who were stage IE or IIE was 54%.⁴⁷

In summary, early-stage colonic lymphomas should be resected. Late-stage disease should be operated on to obtain tissue, bypass obstructions, and resect perforations. All patients should be presented and managed by a multidisciplinary tumor board that can assess the tumor and patient characteristics, recommend further chemotherapy or radiation, and identify appropriate clinical trials.

SPECIAL SITUATIONS

Posttransplantation lymphoproliferative disorder (PTLD) is a complication of solid organ transplant. PTLD is a term that includes many disease processes such as plasmacytic hyperplasia, Hodgkin lymphoma, diffuse large B-cell lymphoma, Burkitt lymphoma, and T-cell neoplasms. In pediatric and adult transplant patients, it is the first and second most common malignancy.^{48,49} Most lymphomas associated with PTLD are of B-cell origin (85%) and are related to Epstein-Barr virus (EBV; 80%).^{50,51} The highest risk for developing PTLD is in the first year after transplant.⁵² Management of PTLD is dependent on the patient's clinical status, transplant function, histologic subtype, grade, stage, and site of the lesion.⁵² In a large retrospective review from the University of Michigan, 78 patients developed PTLD over a 33-year period (1.1% of all transplants).⁵³ Survival rates were comparable to patients without transplants in the SEER (Surveillance, Epidemiology, and End Results) population sample who underwent treatment.⁵³

Chronic immunosuppression of patients with inflammatory bowel disease has led to concerns that they may be at increased risk for lymphoma. There were seven population-based studies on GI lymphoma reviewed for this article.^{5,6} Three studies mentioned IBD and within these studies only two patients were identified with IBD and GI lymphoma.^{5,23,24} Holubar et al identified 15 patients (0.06%) over a 40-year period with IBD in the prebiologic era that had primary intestinal lymphoma.⁵⁴ The 5-year survival rate was 63%. A large population-based case-control study in Denmark and Sweden found no increased risk of NHL or any subtype of NHL in patients with IBD.⁵⁵ IBD and lymphoma is an unusual event and IBD associated with GI lymphoma is exceptionally rare.

Patients with HIV are at increased risk for Kaposi sarcoma, cervical cancer, and non-Hodgkin lymphoma, which are AIDS-defining cancers.⁵⁶ Individuals with HIV had decreasing incidences of Kaposi sarcoma and NHL corresponding to the introduction of HAART.⁵⁷ A 2010 analysis of the HIV/AIDS Cancer Match Study examined the incidence of AIDS-defining and non-AIDS-defining cancers in 472,378 individuals who were cancer free before their AIDS diagnosis.⁵⁸ This study identified decreases in 5-year cumulative incidences in AIDS-defining cancers. NHL showed a decrease from 3.3 in 1980–1989 to 2.2 in 1996–2006. However, cumulative incidences in non-AIDS-defining cancers such as Hodgkin lymphoma, liver, anal, and lung cancer increased reflecting increased longevity in patients with HIV.

CONCLUSION

Colonic lymphoma is a rare diagnosis. Almost half of all colonic lymphomas present emergently and require surgery demanding a high degree of suspicion by the surgeon. Patients who are diagnosed electively benefit from having a tissue diagnosis prior to surgery as well as appropriate imaging. Surgery is the mainstay of treatment for stage I and II disease possibly followed by chemotherapy and radiation. Disseminated disease requires surgery for obstruction, perforation, and bleeding. A multidisciplinary tumor board should manage all aspects of care of patients with colonic lymphoma. Future discoveries in molecular genetics, tumor analysis, and immunohistochemistry will continue to advance the management of colonic lymphoma.

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