

## CASE REPORT

# Primary follicular lymphoma of colon: A case series and review of literature

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**Abstract**

Follicular lymphoma of the colon is rare, accounting for 1% to 2% of cases in the gastrointestinal tract. Despite the absence of randomized clinical trials, NCCN stage III and IV colonic follicular lymphomas are routinely treated with chemotherapy with good clinical response. We present 2 cases of advanced stage follicular lymphoma of colon that were effectively treated with bendamustine-based chemotherapy regimens.

**KEY WORDS**

chemotherapy, colon lymphoma, non-Hodgkin's lymphoma

## 1 | INTRODUCTION

Follicular lymphoma (FL) of the colon is rare, and hence, treatment protocols have not been standardized. We report 2 cases of advanced stage FL of colon treated with obinutuzumab and rituximab-based chemotherapy regimens with resolution of tumor and progression free survival.

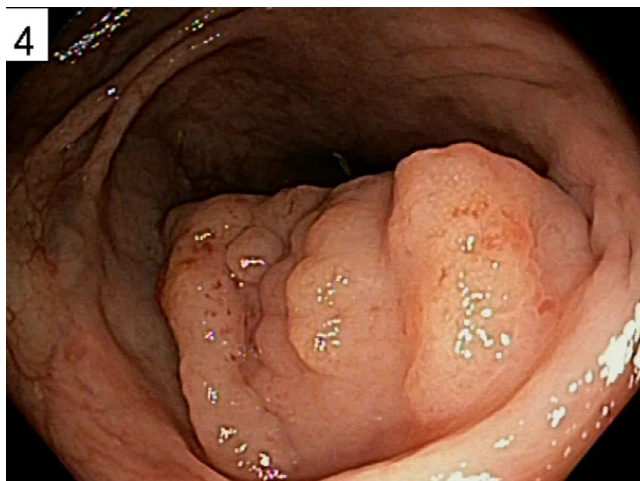
The gastrointestinal (GI) tract is the most common site of extranodal non-Hodgkin's lymphoma (NHL), representing 30%–70% of all extra nodal lymphomas.<sup>1</sup> Follicular lymphoma (FL) is the second most common type of NHL and the most common form of indolent lymphoma. Despite its relative prevalence in the Western population, FLs are rare in the GI tract. The stomach is the most common site of involvement, followed by the small intestine and, rarely, the colon.<sup>2,3</sup> Reports of FLs involving the colon remain limited. We present two cases of FL of the colon, with a review of the clinical features, immunophenotyping, and treatment options.

## 2 | CASE 1

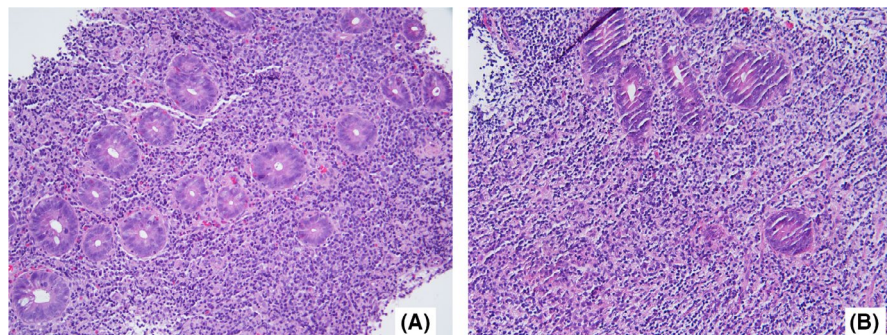
A 69-year-old woman with a history of left-sided ductal carcinoma treated in situ with lumpectomy, radiation, tamoxifen, diabetes mellitus, essential hypertension, and a 3-mm hyperplastic polyp in the sigmoid colon on colonoscopy 5 years ago returned for a surveillance colonoscopy. At the time of presentation, she denied any history of abdominal pain, nausea, vomiting, melena, hematochezia, or weight loss. On colonoscopy, a protuberant ileocecal valve was noted with an 8-mm area of overlying adenomatous appearing mucosa (Figure 1). Biopsies of the mass were obtained with pathology, demonstrating low-grade (1–2) follicular lymphoma. Immunohistochemistry was positive for CD20, CD10, bcl-2, and bcl-6 and negative for CD5. Computed tomography (CT) of the chest, abdomen, and pelvis showed mesenteric adenopathy. A subsequent positron emission tomography (PET) scan revealed hypermetabolism within an enlarged lymph node in the mesentery,



**FIGURE 1** Protuberant ileocecal valve was with the proximal lip of the valve (cecal side) demonstrating an approximately 8-mm adenomatous appearing mucosa extending into the terminal ileum



**FIGURE 2** Large, sessile, 40-mm polyp in the hepatic flexure of the colon



**FIGURE 3** A and B, Colonic mucosa with dense, band-like lymphoid infiltrate of small- to medium-sized cells. The lamina propria is expanded by an increased number of lymphoid cells with significant crypt destruction

and no other areas of hypermetabolic activity were seen. A bone marrow biopsy did not show any evidence of lymphoma. The patient was followed up by medical oncology, and given that the hypermetabolic node was not contiguous

to the ileocecal valve, the tumor was staged IV-A, as per National Comprehensive Cancer Network (NCCN) guidelines. A “watch-and-wait” approach was favored for asymptomatic, low-grade lymphoma.

The patient was routinely followed up for 3 years without evidence of disease progression. However, a CT scan of the abdomen and pelvis 3 years after the initial diagnosis demonstrated disease progression, including mesenteric and retroperitoneal adenopathy, possible lymphoma involving the terminal ileum, and concern for splenic involvement. A follow-up PET scan reported hypermetabolic mesenteric, retroperitoneal, and paraesophageal adenopathy. There was increased tracer uptake in the terminal ileum which was concerning for small-bowel lymphoma. Immunohistochemistry of a right inguinal lymph node biopsy was positive for CD20, CD10, and bcl-6; weakly positive for bcl-2; and negative for CD5 and CD21. She was treated with a combination of obinutuzumab and bendamustine. After 4 cycles of therapy, a repeat PET scan showed interval resolution of hypermetabolic activity in the abdominopelvic lymph nodes and spleen. The patient was lost to follow-up after completing only four cycles.

### 3 | CASE 2

A 51-year-old woman with a history of essential hypertension and intermittent constipation was referred to gastroenterology for surveillance colonoscopy. Colonoscopy revealed two polyps—5mm and 7mm in the ascending and transverse colon, respectively—that were removed. A large, sessile, 40-mm hepatic flexure polyp (Figure 2) was lifted with submucosal injection and resected in a piecemeal fashion. Histopathology confirmed tubular adenoma in the transverse colon and grade (1–2) follicular lymphoma in the ascending colon and hepatic flexure. Immunohistochemistry

was positive for CD20, CD10, bcl-2, and bcl-6 but negative for CD5 and bcl-1. CT of the chest, abdomen, and pelvis revealed prominent mesenteric adenopathy. A subsequent PET scan reported mildly increased tracer uptake in the enlarged

mesenteric lymph nodes. Repeat colonoscopy 6 months later demonstrated an irregular appearing ileocecal valve with a large sessile lesion distal to the valve that was biopsied. Histopathology was positive for low-grade (1–2) follicular lymphoma (Figure 3). A bone marrow biopsy was suspicious for lymphomatous involvement, although flow cytometry was negative. The tumor was stage IV, as per NCCN guidelines. She was initiated on a bendamustine-rituximab (BR) regimen. After completion of 6 cycles of BR therapy, the patient has been disease-free for 2 years on follow-up with surveillance imaging.

## 4 | DISCUSSION

Follicular lymphoma is a common subtype of NHL, arising from the germinal center of B cells. It typically arises in the lymph nodes and involves the liver, spleen, and bone marrow. Skin, salivary glands, and reproductive and gastrointestinal systems are common sites of extranodal involvement.<sup>2</sup> FL of the GI tract is rare and constitutes less than 7% of all NHLs<sup>4</sup> and is more common in the duodenum (89%), jejunum (40%), and ileum (22%), whereas colorectal FLs account for 1% to 2% of all cases.<sup>5</sup> The high frequency of small intestinal involvement is thought to be related to the relative abundance of lymphoid follicles.<sup>4</sup>

The clinical manifestations of FLs are nonspecific and depend on the area involved. The most common presentation of a gastrointestinal FL is an obstructing lesion. However, similar to our reported cases, patients may be asymptomatic and present with incidental findings on endoscopy or imaging studies. The macroscopic appearance of colorectal FLs can be papular, polypoid, flat elevated, or ulcerated. Progressing from a papular to flat elevated appearance is believed to be related to an increase in the number of infiltrated lymphoma cells.<sup>6</sup> The diagnosis of FL is based on histology, immunophenotyping, *bcl-2* gene expression, and detection of *t(14;18)* by a polymerase chain reaction.<sup>7</sup> Microscopically, most FLs are composed of small cleaved lymphocytes with a varying mixture of large cells. The translocation *t(14;18) IgH/bcl-2* is the molecular hallmark of FL seen in up to 75% of cases.<sup>8</sup> As observed in both our cases, most colonic FLs express CD10, CD20, and *bcl-6* but do not express CD3, CD5, CD23, CD43, or cyclin D1.<sup>4</sup> Proliferative lymphoid lesions are morphologically similar to FL. They can be distinguished from FL by the conspicuous absence of *bcl-2* expression.<sup>9</sup> The gross appearance of FLs is similar to multiple lymphomatous polyposis that has a poor prognosis and requires aggressive treatment.<sup>10</sup> Immunophenotyping with immunostaining is required to distinguish between them. Mantle cell lymphomas express CD5 and cyclin D but do not express CD10, whereas FLs express CD5 and CD10 but do not express cyclin D.<sup>11</sup>

The NCCN stages primary GI lymphoma using the Lugano criterion, which is based on the older Ann-Arbor staging system.<sup>12</sup> Limited stage (Ann Arbor I or II) FL is relatively uncommon. When comparing treatment approaches, there are no differences in the overall survival with chemotherapy, radiation therapy, combination therapy, or observation.<sup>13</sup> As such, a watch-and-wait approach is appropriate in most situations. In advanced stage (Ann Arbor III or IV) FL, the therapeutic approach is dependent on the patients' symptoms and tumor burden. The degree of tumor burden is assessed by the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria.<sup>14</sup> There are no randomized controlled clinical trials (RCTs) that have compared the rituximab-chemotherapy regimen to the watch-and-wait strategy in asymptomatic primary follicular lymphoma patients with a low tumor burden.<sup>15</sup> In one RCT comparing rituximab alone with observation alone, there was no difference in the overall survival at 3 years. In symptomatic patients with a high tumor burden, a phase 3 trial demonstrated better efficacy with the bendamustine-rituximab regimen than rituximab, cyclophosphamide, vincristine, and prednisone (R-CHOP).<sup>16</sup> And another phase-3 study found BR to be noninferior to R-CHOP.<sup>17</sup> The GALLIUM trial demonstrated that obinutuzumab-based immunochemotherapy and maintenance therapy resulted in longer progression-free survival than rituximab-based therapy, but high-grade adverse events were more common with obinutuzumab-based chemotherapy.<sup>18</sup> Both of our patients with stage IV disease demonstrated a good response to obinutuzumab- and rituximab-based chemotherapy, respectively. In relapsed and refractory FL, other alkylating agents, such as fludarabine, and kinase inhibitors have been shown to be effective. Overall, the prognosis of FL is dependent on clinical and laboratory characteristics, with age >60 years, elevated beta-2 microglobulin, hemoglobin <12 g/dl, bone marrow involvement, and lymph node diameter >6 cm shown to be independent risk factors for progression-free survival.<sup>19,20</sup>

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The authors have no financial or nonfinancial conflict of interest that is relevant to the manuscript.

## AUTHOR CONTRIBUTIONS

Abdul Mohammed: Conception, design, and preparation of the manuscript. Farnaz Shariati: Conception, design, and preparation of the manuscript. Neethi Paranj: Conception, design, and preparation of the manuscript. Nisheet Waghray: Review of criteria and final approval of the manuscript.

## ETHICAL APPROVAL

This material is the authors' original work, which has not been published elsewhere. It is not being considered for publication elsewhere. All authors made meaningful contributions to the paper.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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