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Case report

# Primary Lymphoma of the Distal Ileum: Case Presentation and Literature Review

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## Abstract

**Introduction:** Primary lymphoma of the small intestine is an uncommon neoplasm representing a small subset of extranodal non-Hodgkin lymphomas. Diagnosis is often challenging due to nonspecific symptoms, including abdominal pain, weight loss, and anemia, and may present as intestinal obstruction in advanced cases. Endoscopy with biopsy and computed tomography are key diagnostic tools, though surgical exploration is required in some instances. **Case report:** We describe a patient diagnosed with marginal zone B-cell lymphoma (MALT type) in the distal ileum, detected incidentally during colonoscopy. The patient underwent treatment with R-bendamustine/rituximab, achieving complete remission, with clinical and endoscopic follow-up over 8 years showing no recurrence. **Conclusions:** This review summarizes current evidence on anatomical distribution, clinical manifestations, radiologic and endoscopic findings, prognosis, and treatment strategies for intestinal lymphomas. Recent studies show that B-cell lymphomas carry a better prognosis than T-cell types, and that combining surgery with chemotherapy improves survival in localized disease. The findings underscore the importance of evaluating the distal ileum during routine colonoscopy, as thorough assessment may facilitate earlier diagnosis and improve patient outcomes.

## Keywords

Lymphoma, intestine, B-cell lymphoma, diagnosis, endoscopy, MALT lymphoma, prognosis.

## INTRODUCTION

In the intestine, lymphoid tissue is distributed under the designation GALT (gut-associated lymphoid tissue), which constitutes an essential component of the immune system and is designed to address the constant exposure to a high antigenic load derived from the diet and the commensal microbiota. This system is divided into two main compartments: organized GALT, which includes Peyer's patches and mesenteric lymph nodes, and diffuse GALT, composed of intraepithelial lymphocytes (IELs) and lamina propria lymphocytes (LPLs). Organized GALT acts as a key inducer of the intestinal immune response, whereas diffuse GALT functions as a direct effector of specific immune and tolerance responses. This structure allows discrimination between invasive antigens and innocuous components, thereby promoting intestinal protection and homeostasis[1].

The GALT of the ileum is characterized by a greater abundance of Peyer's patches, appearing as prominent organized lymphoid follicles. These patches are located primarily on the antimesenteric surface of the intestinal mucosa. Being more exposed to a higher antigenic load from intestinal contents (diet and microbiota), the ileum plays a more active role in the generation of adaptive immune responses. Peyer's patches in the ileum are key to capturing luminal antigens through specialized M cells[1,2].



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Interactions among T and B lymphocytes, dendritic cells, and factors such as transforming growth factor beta (TGF-β), a proliferation-inducing ligand (APRIL), and B-cell activating factor (BAFF) are critical for the differentiation and proliferation of B cells in the small intestine. APRIL and BAFF are cytokines of the tumor necrosis factor (TNF) family that play a crucial role in regulating the immune system, particularly in B-cell survival, activation, and differentiation. Both molecules are essential for mucosal immunity and the production of immunoglobulin A (IgA), which is key in Peyer's patches and other areas of the GALT[3].

Hematologic neoplasms include leukemias, lymphomas, myeloproliferative neoplasms, plasma cell dyscrasias, histiocytic tumors, and dendritic cell neoplasms. The classification currently in force is that of the World Health Organization (WHO) 2022[4]. Lymphomas are a heterogeneous group of neoplasms arising from lymphohematopoietic tissues and originating from B cells, T cells, or NK/T cells. They are divided into two main groups: Hodgkin disease and non-Hodgkin lymphoma. Hodgkin lymphoma is composed of B cells known as Reed-Sternberg cells; these very large cells are multinucleated or have a bilobed nucleus with prominent inclusion-like nucleoli. Reed-Sternberg cells tend to be CD30- and CD15-positive and are usually CD20- and CD45-negative[5].

Although most lymphomas are located in lymphoid organs (lymph nodes, spleen, thymus, Waldeyer's ring), up to 15%–48% of lymphomas arise in extralymphoid tissues or organs. Most of these belong to the non-Hodgkin lymphoma group, as extranodal presentation of Hodgkin disease accounts for less than 1% of cases. The extranodal sites most frequently affected by lymphoma are the gastrointestinal tract, skin, and bone. Gastrointestinal lymphomas represent approximately 30%–44% of extranodal lymphomas[6].

The stomach is the most frequently involved site within the gastrointestinal tract, followed by the small intestine and, lastly, the colon. These account for 1%–7% of malignant tumors of the stomach, 20% of those of the small intestine, and 0.4% of those of the large intestine. Most are non-Hodgkin lymphomas, with B cells predominating over T cells[7]. Primary lymphoma of the small intestine is an infrequent entity within non-Hodgkin lymphomas (NHL), representing only a small fraction of these tumors and an even smaller proportion within the spectrum of gastrointestinal tract lymphomas, where most involve the stomach. Its low incidence, combined with nonspecific clinical presentation and the difficulty of accessing the small intestine with conventional endoscopic methods, makes early diagnosis challenging. Advances in colonoscopy and distal ileal exploration in recent years have allowed better characterization of these neoplasms; however, systematic evaluation of the distal ileum is neither mandatory nor routine in endoscopic practice, which may hinder diagnosis[8].

Due to its low worldwide frequency, treatment—whether surgery plus chemotherapy or chemotherapy alone—remains controversial. Clinical follow-up, whether conventional endoscopic surveillance or using other techniques, is still evolving. These considerations underscore the clinical and academic interest of the present case.

## CLINICAL CASE

This is a 49-year-old female patient first evaluated on November 4, 2015, during a colonoscopy requested for the assessment of nonspecific abdominal pain. Colonoscopy findings were normal; however, in the distal ileum, approximately 3 cm from the valve, nodular-appearing lesions were identified over an extension of approximately 6 cm, from which biopsies were difficult to obtain (**Figure 1**).

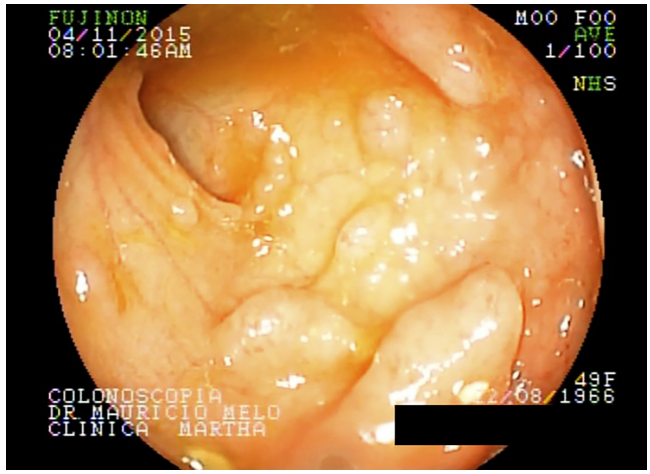



**Figure 1.** Year 2015. Appearance of the distal ileum with multiple nodular-appearing lesions. Pre-treatment image without histologic diagnosis. Author's File.

Biopsy showed reactive lymphoid hyperplasia. Given the nonspecific biopsy findings, a repeat ileocolonoscopy was suggested; however, the patient did not attend follow-up until April 26, 2017, when a new ileocolonoscopy was performed. In the distal ileum, approximately 3 cm from the ileocecal valve and extending for about 4 cm, irregular polypoid-appearing tissue with a rubbery consistency was found, making biopsy difficult; therefore, ten biopsies were obtained (**Figure 2**).

Pathology reported nodular ileitis, extranodal marginal zone B-cell lymphoma (MALT), with Ki-67: 1%, and positivity for CD20, CD5, CD43, and CD23. The hematologist staged the disease as stage IV (the classification system used was not specified), with involvement of the

ileum and bone marrow. The patient received the first cycle of chemotherapy with R-bendamustine/rituximab on July 7, 2017, followed by four similar cycles, which were completed on October 17, 2017. In May 2017, an abdominal computed tomography (CT) scan was normal, and a chest CT was also normal.

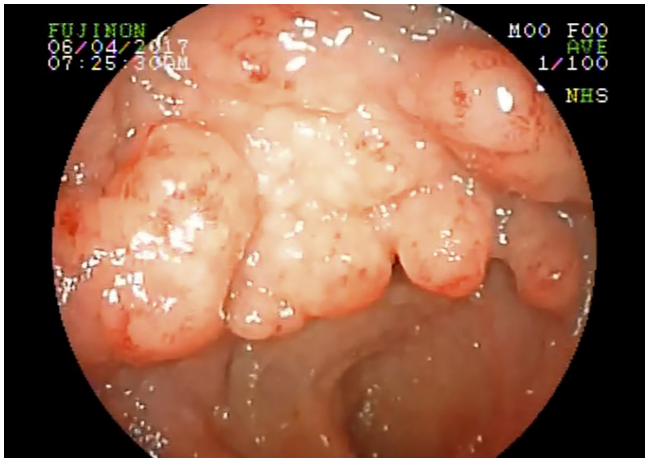



**Figure 2.** Year 2017. Distal ileum with irregular polypoid-appearing tissue, several with superficial erosions. Pre-treatment and diagnostic image. Author's File.

On follow-up colonoscopy on September 22, 2017, the ileal description revealed ileal mucosa in the process of healing. Biopsies were negative for malignancy, while ileal mucosal fragments showed reactive and cicatricial changes. In February 2018, ileocolonoscopy showed that the ileum appeared morphologically normal, and the previously described lesions now appeared as normal Peyer's patches (**Figure 3**). Biopsies demonstrated an infiltrate of lymphocytes with variable morphology that did not suggest monoclonality, and no evident lymphoepithelial lesion was identified. The hematologist noted that there was no evidence of a hematolymphoid lesion.

On September 9, 2018, the following complete blood count was reported: hemoglobin (Hb) 12.7; leukocytes 4,070; neutrophils 2,380; platelets 280,000. Ultrasound revealed cholelithiasis without cholecystitis, and lactate dehydrogenase (LDH) was 178.8 (normal value [NV]: 214 IU/L). On March 3, 2019, chest and abdominal CT scans showed cholelithiasis, with otherwise normal findings. On August 18, 2019, upper gastrointestinal endoscopy (EGD) showed nodular antral gastritis, while biopsy revealed the formation of lymphoid aggregates with scant forms of *Helicobacter pylori*. Eradication therapy was prescribed with esomeprazole 20 mg (two daily), amoxicillin 500 mg (four daily), and clarithromycin 500 mg (two daily) for 14 days. Ileocolonoscopy was normal, while ileal biopsies indicated nonspecific chronic ileitis and were negative for granulomas or malignancy (**Figure 4**).

At endoscopic follow-up on October 22, 2020, gastric biopsies showed chronic gastritis with mild acute activity, multifocal atrophy, and complete-type intestinal metaplasia, with *H. pylori* negativity. Ileocolonoscopy in October 2020 showed a normal appearance of the distal ileum. Three biopsies were obtained (**Figure 5**). Ileal biopsies revealed edema, increased interstitial infiltrate, and the presence of lymphoid aggregates, some with reactive centers. The interpretation was chronic ileitis. At endoscopic follow-up in February 2025, the ileum was found to be normal (**Figure 6**).

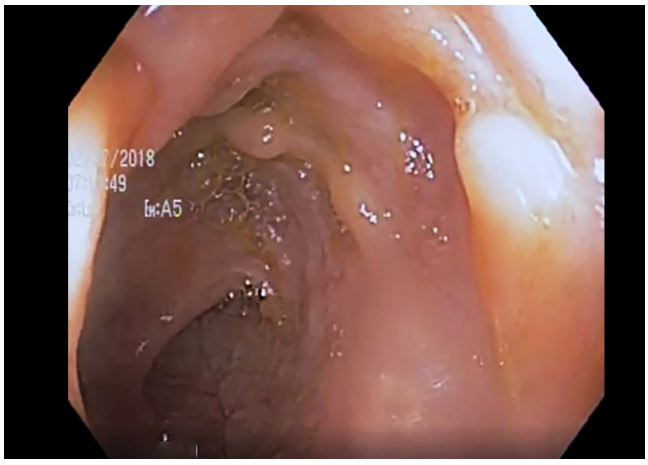


**Figure 3.** Year 2018. Distal ileum with normal appearance. Post-treatment image No. 1, normal. Author's File.

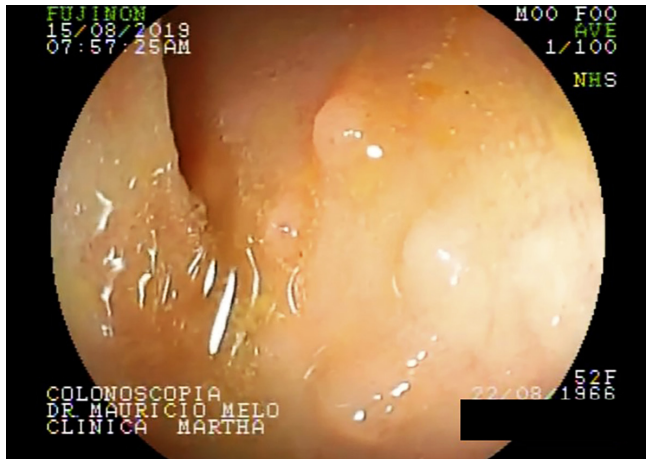



**Figure 4.** Year 2019. Distal ileum with Peyer's patches of normal appearance. Post-treatment image No. 2. Author's File.

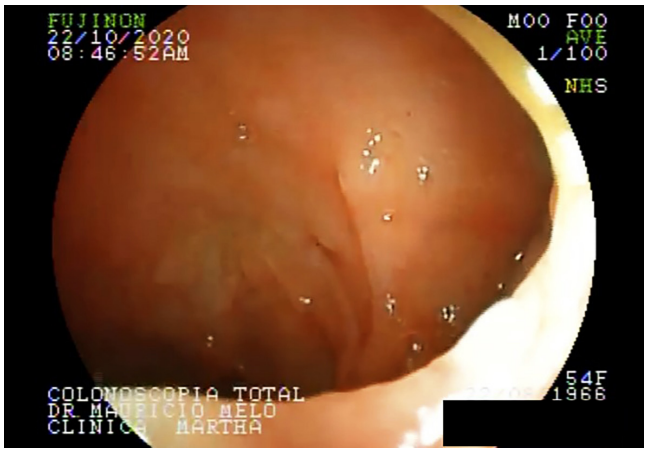



**Figure 5.** Year 2020. Panoramic view of the distal ileum at the edge of the ileocecal valve. Post-treatment image No. 3. Author's File.

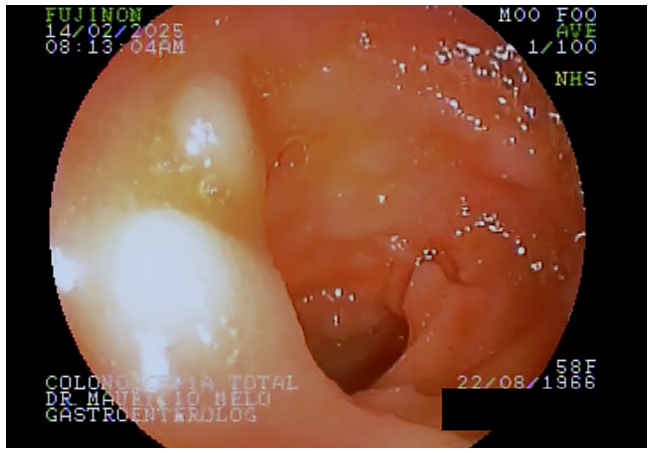



**Figure 6.** Year 2025. Distal ileum with normal appearance. Post-treatment image. Author's File.

## DISCUSSION

Clinical diagnosis is not straightforward, as in uncomplicated cases of intestinal lymphoma the symptoms include persistent abdominal discomfort, fatigue and progressive weight loss, diarrhea or changes in bowel habits, and mild to moderate anemia with chronic subclinical bleeding. In cases with severe complications, patients present with obstructive symptoms such as abdominal distension, absence of bowel movements, and vomiting. When presentation includes perforation, fever and signs of septic shock are added to the aforementioned symptoms[9].

Facundo Navia and Manrique emphasize that primary lymphoma of the small intestine accounts for only 1%–4% of malignant tumors of the digestive tract. The lymphoma described in their publication was diagnosed after multiple medical consultations and imaging studies, which is consistent with the diagnostic challenge described in the literature[10]. In the series by Ge Z, the anatomic distribution of intestinal lymphomas (87 cases) showed a predominance in the distal ileum: 70.3% (within the 100 meters proximal to the ileocecal valve), followed by the jejunum: 16.2%, with multiple involvement of the small intestine in 5.4%. The greater involvement of the ileum is likely due to the higher concentration of lymphoid tissue in this region[11].

The endoscopic presentation of intestinal lymphoma is variable and may mimic other conditions such as Crohn's disease, intestinal tuberculosis, or even adenocarcinoma[12]. In up to 51.4% of cases, plaques or flat lesions predominate; elevated lesions occur in 20.7%, exophytic masses in 12.9%, and elevated lesions with ulceration in 9.3%. More aggressive lymphomas, such as diffuse large B-cell lymphoma (DLBCL), usually present with fungating or protruding lesions with ulcers[13].

According to a retrospective study, the distal ileum is the most frequent location of intestinal lymphomas, probably due to the abundance of lymphoid tissue in this region[11]. The most common histologic type is diffuse large B-cell lymphoma of the small intestine, characterized by large, pleomorphic cells with high proliferative activity (high Ki-67). It may arise from transformation of a pre-existing MALT lymphoma. It is characterized by CD20 positivity, Bcl-6 positivity, CD10 positivity or negativity, and a high proliferation rate (Ki-67 >50%)[14,15].

Diagnosis requires histopathology and immunophenotyping to differentiate B-cell from T-cell lymphomas, which determines treatment. In the case of MALT lymphomas associated with *H. pylori*, eradication with antibiotics may induce remission, whereas high-grade B-cell lymphomas usually require rituximab-based chemotherapy (R-CHOP)[15,16].

Treatment of primary intestinal lymphoma remains controversial. Retrospective studies have shown that the combination of surgery and chemotherapy improves survival in localized disease[17]. A comparative study reported higher survival rates and lower relapse rates in patients with intestinal DLBCL treated with surgery plus chemotherapy compared with those who received chemotherapy alone[18]. Nevertheless, management should be individualized according to stage, histologic type, and the presence of complications[19].

Gou retrospectively analyzed 116 patients to determine factors related to survival and treatment outcomes and found that unfavorable prognostic indicators included male sex, T-cell lymphoma, age over 60 years (associated

with worse outcomes compared with DLBCL), hypoalbuminemia, diagnosis at the time of intestinal perforation, stages III and IV, and not receiving chemotherapy[19].

In a retrospective study by Kim including 581 cases of primary intestinal lymphoma, favorable outcomes were associated with DLBCL or MALT histology, lymphoma localized to the ileocecal area, low LDH levels, Lugano classification I to III, and absence of fever or weight loss at presentation[20].

The clinical case presented here has several favorable response factors, including female sex, age under 50 years, LDH less than 200 IU, and B-cell MALT-type lymphoma. Endoscopy revealed pseudopolypoid lesions without a mass effect.

With respect to treatment, the case described received chemotherapy alone and showed a favorable outcome after 8 years of follow-up when compared with prior series in which both chemotherapy and surgery were administered. It should be noted that these are retrospective studies and that surgery was used in many cases in the presence of perforation or obstruction. Therefore, only prospective studies with random case selection—such as ours, which was detected at an early stage—could resolve this controversy. However, given the small number of cases and the heterogeneity of diagnostic scenarios, treatment decisions still largely depend on clinical judgment. In the present case, chemotherapy with endoscopic follow-up has proven effective, and in the era of monoclonal antibody-based chemotherapy (rituximab), this approach could potentially contribute to increasing case series in our setting and support chemotherapy-based treatment without surgery.

## CONCLUSION

We reviewed a case of primary small intestinal lymphoma located in the distal ileum, detected during colonoscopy and ileoscopy performed for nonspecific abdominal symptoms. The patient was treated by the hematologist with a combination of R-bendamustine/rituximab for four cycles, resulting in clinical, endoscopic, and histopathologic improvement, and she has remained recurrence-free after eight years of follow-up. Based on the review, favorable factors included age, sex, location, and early-stage diagnosis.

In addition, this case highlights that all colonoscopies should, whenever possible, report intubation of the ileocecal valve and evaluation of the distal ileum. As discussed, early symptoms of these lymphomas are nonspecific, and as demonstrated in the reviewed studies, most primary lymphomas are located in the ileocecal region. Similar diagnoses may be missed if the ileocecal valve is not intubated and the greatest possible length of ileum is not explored during the procedure.

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