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Primary Non-Hodgkin Lymphoma of the Colon. Report of Two Cases and Review of the Literature

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ABSTRACT

Introduction: *Primary colon lymphoma accounts for less than 1% of all colorectal neoplasms and the right colon is the segment most frequently affected. Diffuse large B cell is the most common histological type.*

Objective: *To describe two patients with primary colon lymphoma and to review the available bibliography, emphasizing the diagnostic approach and indications for surgical management.*

Patients and methods: *Two patients, 38 and 62 years old, with primary colon lymphoma are presented. One of them required emergency surgical management, while the other presented symptoms for several weeks, which allowed follow-up in the outpatient clinic. Both were managed with surgical resection and postoperative chemotherapy.*

Discussion: *Seventy percent of primary colon lymphomas occur in the right colon, presentation in the descending colon and rectum is associated with a worse prognosis. Immunosuppression and inflammatory bowel disease are considered the most important risk factors in their development. The most common presenting symptoms are pain, abdominal mass, weight loss, and gastrointestinal bleeding. In patients with resectable lesions, the best treatment approach is the combination of surgical resection and postoperative chemotherapy.*

Conclusions: *Primary colon lymphoma is a rare entity that requires a multidisciplinary approach. In patients who do not present with surgical urgency, abdominal tomography and PET-CT provide valuable information to define the feasibility and extent of surgical resection, which should be complemented with postoperative chemotherapy.*

Keywords: *Lymphoma; Extranodal; Colon; Surgery; Chemotherapy*

INTRODUCTION

Lymphomas are a malignant entity that originates from hematological cells of lymphoid lineage. They can have an indolent or aggressive behavior, manifesting with lymphadenopathy or solid tumors that can compromise any organ of the body.[1] Ninety percent correspond to non-Hodgkin's lymphomas, which can present extranodal manifestations in one-third of cases and compromise the gastrointestinal tract in 5-15%.[2] The stomach is the most frequently involved organ in approximately 50% of cases, followed by the small intestine and esophagus.[3]

Lymphomas represent 0.2-0.8% of all colorectal neoplasms, most frequently affect the right colon and the most common histological variant is the diffuse large B cell lymphoma (DLBCL).[2,3]

The objective of this study is to describe two patients with lymphoma of the right colon treated surgically, as well as to review the bibliography, highlighting the diagnostic approach and indications for the surgical management of primary colon lymphoma (PCL).

CASE 1

A 38-year-old man with no significant medical history attended the emergency room for abdominal pain in the right iliac fossa associated with asthenia and adynamia. He reports changes in bowel habits lasting 1 month associated with occasional melena, without weight loss. On initial examination, he was found to be tachycardic, pale and with mild pain on palpation in the right abdo-

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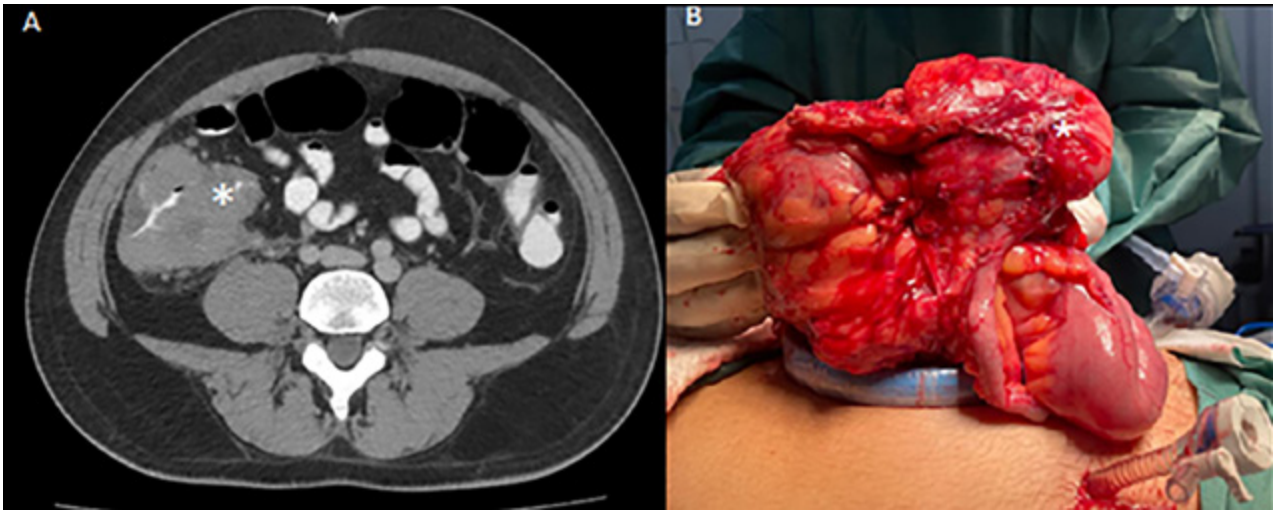

Figure 1: A) Double contrast abdominal tomography showing a mass in the cecum (*). B) Intraoperative image after the release of the right colon by laparoscopy, prior to surgical resection.

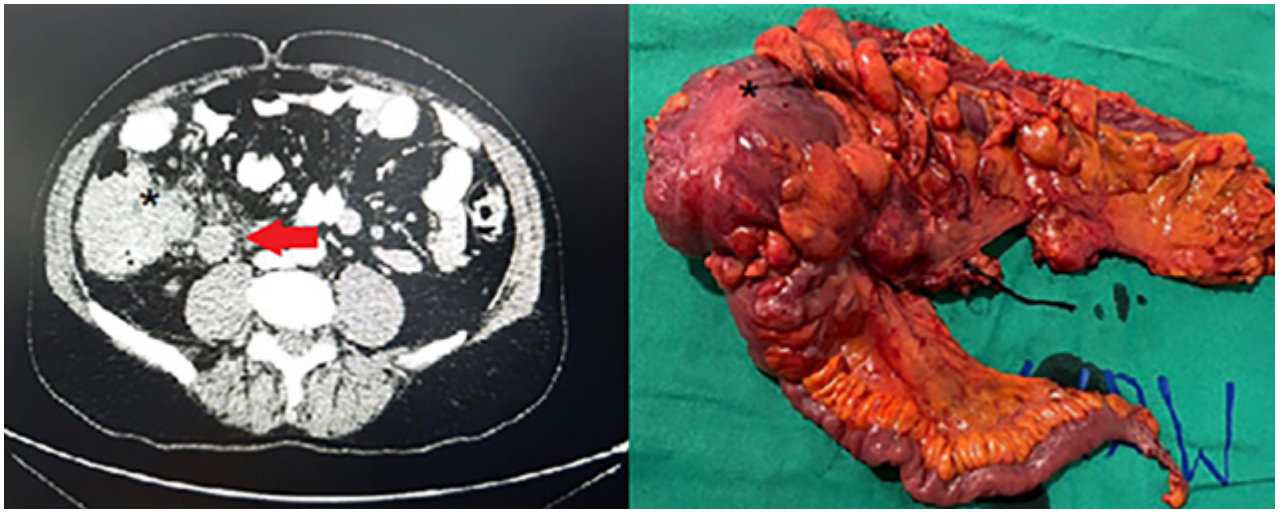

Figure 2: A) Double contrast abdominal tomography showing a mass in the ascending colon (*) associated with regional lymph nodes (arrow). B) Surgical specimen with a tumor in the ascending colon and thickened mesocolon. Right colic vessels marked with silk threads.

men, without signs of peritoneal irritation. In the initial lab exams, severe anemia and fresh blood in the stool are found. There are no signs of systemic inflammatory response. Hemodynamic stabilization is performed and transfusion support is provided.

Contrast tomography of the abdomen and pelvis shows irregular thickening of the cecum, ascending colon and terminal ileum, without structural changes of the pericecal fat and lymphadenopathies due to secondary involvement. Colonoscopy reports a polypoid mass in the cecum that covers almost 96% of the lumen and prevents visualization of the ileocecal valve and the appendicular orifice. The mucosa of the ascending, transverse, and descending colon is normal.

Due to the impending obstruction and associated lower gastrointestinal bleeding, a laparoscopic right colectomy with extracorporeal ileotransverse anastomosis was performed. There was no free fluid in the abdominal cavity and no liver metastases. The patient evolved satisfactorily and was discharged. The pathology result reported a DLBCL (Fig. 1).

CASE 2

A 62-year-old male patient, with no relevant pathological medical history, consulted for mild postprandial epigastric pain radiating to the thoracolumbar region and 8-kg weight loss lasting 6 months. Three months after the onset of symptoms, hematochezia, abdominal distension, and pain progression were associated, so opioid management was started. Colonoscopy showed a 6 cm mass with necrotic areas and bleeding stigmata at the junction

TABLE 1: DAWSON'S CRITERIA FOR THE DIAGNOSIS OF PRIMARY COLON LYMPHOMA.[6]

1. Absence of palpable superficial lymphadenopathies.
2. Absence of mediastinal node enlargement on chest x-ray.
3. Normal white cell count and differential in the evaluation of peripheral blood.
4. Lesion only confined to the bowel and regional lymphadenopathies.
5. Absence of liver or spleen involvement, except for the involvement by local extension of a gastrointestinal tumor.

TABLE 2: MODIFIED STAGING OF PRIMARY GASTROINTESTINAL NON-HODGKIN LYMPHOMA.[8]

STAGE I: Tumor confined to the gastrointestinal tract.
STAGE II-1: Tumor affects regional lymph nodes.
STAGE II-2: Involvement includes beyond the regional lymph nodes.
STAGE III: Tumor with involvement of other organs in the abdomen (liver, spleen), or beyond the abdomen (thorax, bone marrow).

of the ascending colon and the cecum, above the ileocecal valve. The biopsy reported acute necroinflammatory material with bacterial superinfection, without tumor. No abnormalities on physical examination. A new colonoscopy revealed a mamelon-like tumor in the middle third of the ascending colon measuring 60 × 60 × 60 mm that compromised 100% of the circumference and obstructed the lumen in 75%, with a Kudo Vn glandular pattern. The pathology report informed infiltration of the lamina propria by a neoplasm made up of large cells, with lumpy chromatin, some with nuclei with convolution, findings suggestive of infiltration of large cell lymphoma. Abdominal tomography revealed a solid expansive 47-mm transmural lesion in the middle third of the ascending colon, with a neoplastic appearance, and multiple lymphadenopathy in the mesocolon. In addition, a 50 mm lymph node cluster was closely related to the second and third portions of the duodenum. Chest tomography showed no lesions and upper gastrointestinal endoscopy revealed mild extrinsic compression in the second portion of the duodenum. A laparoscopic extended right colectomy was performed, finding a tumor in the proximal third of the ascending colon measuring 12 × 12 × 12 cm that infiltrated the serosa, associated with a 50 × 50 × 50 mm lymph node conglomerate at the origin of the ileocolic vessels, adhered to the second and third portion of the duodenum. The difficulty to dissect it laparoscopically, caused conversion. The patient evolved favorably and was discharged. The pathological report showed DLBCL, of centrogerminal origin by immunohistochemistry, with lymph node conglomerates and 39/50 pericolonic lymph nodes compromised by the tumor (Fig. 2).

DISCUSSION

Non-Hodgkin PCL is a rare entity with a variable presentation, from indolent to presenting in advanced stages that require emergency surgical management.[4] Fifty percent of cases are located in the cecum and 20% in the ascending colon. Its presentation in the descending colon and rectum is associated with a worse prognosis, with a mean survival 68 months lower than that of lymphoma of the right colon.[4]

Immunosuppression and inflammatory bowel disease are considered the most important risk factors in the development of PCL.[5] The mean age of presentation is 55 years and age older than 60 years is a worse prognostic factor.[2,4]

The most frequent presenting symptoms, according to the case series described, are abdominal pain (71.4%), abdominal mass (54%), weight loss (43%), gastrointestinal bleeding (27%), change in bowel habits (14.3%), intestinal obstruction (9.6%) and anemia (7.6%).[4,5]

In the first case described, the patient presented a rapidly evolving picture, with imminence of intestinal obstruction and bleeding from the lower gastrointestinal tract that required transfusion support, for which surgical management was indicated. In the second case, symptoms progressed slowly, with weight loss, abdominal pain, and non-massive lower gastrointestinal bleeding.

For the diagnosis of PCL it is necessary to rule out systemic lymphoma with colonic involvement, since the treatment and prognosis are different. In 1961, Dr. Dawson proposed the criteria that must be fully met to diagnose PCL (Table 1).[5,6] At present, these criteria are less widely used due to the advancement of diagnostic tests that facilitate the study of high-grade lymphomas.

In 1971, in Ann Arbor, Michigan, a staging system was created for Hodgkin's lymphoma, which was later also used for non-Hodgkin's lymphoma.[7] In 1977 the Ann Arbor classification was modified, creating a specific staging for non-Hodgkin lymphoma of the gastrointestinal tract (Table 2).[8]

The initial study of a patient with suspected gastrointestinal tract lymphoma should be accompanied by testing for HIV and other sexually transmitted diseases.[5] In cases that present without surgical urgency, it is recommended to perform biopsies with sufficient histological material, ideally a Trucut biopsy. To increase the diagnostic yield, it

is recommended to divide the sample in two, one part in formalin for histopathological and immunohistochemical analysis and the other in serum for flow cytometry.[9]

Imaging studies

In the diagnostic imaging approach, contrast-enhanced abdominal tomography is considered the most useful method, due to its anatomical detail, low technical requirements and short acquisition time, as well as its ability to identify locoregional adenopathies and estimate the size and extension of the lesion.[10] Although there are no pathognomonic findings, several patterns of presentation have been described. In a series of 15 cases, these patterns were grouped into 3: focal mass, focal infiltrative and diffuse infiltrative.[11] However, none of them is characteristic or exclusive and the most frequent finding is a circumferential and concentric thickening of the colonic wall. This was the case in the first patient presented, who had a tumor extended to the cecum and ileocecal valve, without desmoplastic involvement of the fat and with decreased intestinal lumen without obstruction. These lesions also present to a lesser extent as an exophytic mass, with mucosal nodularity or fold thickening, which sometimes generates focal stenosis, aneurismal dilatation, ulceration, fistula formation, and intussusception. In case of extracolonic extension or significant lymph node involvement, the mass effect on neighboring structures can be observed, as occurred in the second case, at the duodenal level.[12]

The differential diagnosis with colon adenocarcinoma can be complex, however, the existence of well-defined tumor margins and the absence of compromise of adjacent structures, perforation and desmoplastic reaction, help to distinguish it. Although both can cause segmental stenosis, intestinal obstruction is less frequent in lymphoma, due to the absence of adjacent desmoplastic reaction and the predominantly submucosal infiltration that causes weakness of the internal muscular wall.[13]

The performance of magnetic resonance imaging is limited, especially in the involvement of the ascending colon or cecum, although it is of moderate importance in rectal lesions. However, there are no findings that differentiate it from other tumors in this location.[14]

The role of PET/CT in diagnosis is uncertain, since it is common to find hypercaptant foci in the cecum in benign inflammatory conditions such as amoebic colitis and inflammatory bowel disease, among others. It has been proposed that the values of SUV max (maximum standard uptake values) greater than 11 g/ml could discriminate between benign and malignant lesions. However, there are no parameters that differentiate the metabolic behavior of lymphoid-type neoplastic lesions from the more prevalent colon adenocarcinoma, so it should always be interpreted together with the anatomical findings.[15] PET/CT is of great importance in patients who already have a diagnosis of PCL, to achieve adequate tumor staging. However, it is necessary to take into account the poor uptake of 18DFG in low-grade type B lymphomas and in marginal lymphomas.[16]

Endoscopic studies

Colonoscopy plays a very important role in colonic neoplasms, since in addition to describing the lesion and its extension, it allows biopsies to be taken for histological classification. However, there are few reports in PCL and there is no consensus for its endoscopic classification.

In general, according to the endoscopic findings of the colonic mucosa, five crypt patterns can be distinguished following the Kudo classification: type I and II, which are not neoplastic, type IIIS, IIIL and IV, which correspond to intramucosal neoplasms, and type V, with distorted crypts (VI) or amorphous surface (VN), suggestive of carcinoma.[17]

A study of PCL in Korea, analyzed the colonoscopies of 78 patients.[18] According to the endoscopic findings, this pathology was only suspected in 15.4% of the studies; 80.7% of patients had some variant of B-cell lymphoma and 19.3% a T-cell lymphoma. Based on the endoscopic findings, the authors classified the lesions into 5 categories: polypoid mass (46.2 %), ulcerated polypoid mass (23.1%), ulcerative-infiltrative mass (11.5%), ulcerative mass (12.8%) and infiltrative mass (6.4%). In T-cell lymphomas, the most frequent endoscopic type (80%) were infiltrative or ulcerative-infiltrative lesions, while 54% of B lymphomas manifested as polypoid masses, as described in the literature, predominantly prevalent in the MALT subtypes of mantle cells and in lymphomatous polyposis.[19]

The role of endoscopic ultrasonography in this pathology remains to be established. Its good performance in defining the extent of the lesion and locoregional lymph node involvement is known. The main findings are usually thickening of the second and third layers of the intestinal wall, associated with hypoechoic nodules.[19]

Pathology findings

DLBCL represents the most common type of non-Hodgkin's lymphoma and can be divided into biologically distinct morphologic variants, cell-of-origin variants, and clinical subtypes. In turn, it may be the result of transformation of a pre-existing low-grade lymphoma. In the gastrointestinal tract, it can account for up to two-thirds of lymphoma cases. Macroscopically, ulcerated, elevated or infiltrating lesions are observed, which in some cases

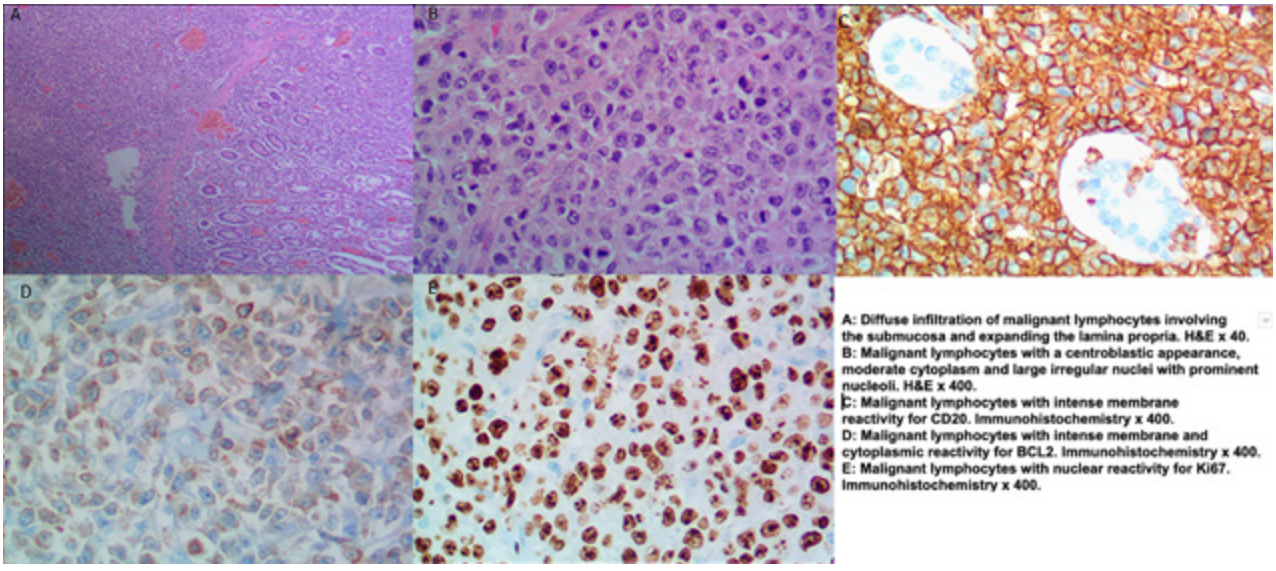

Figure 3: Non-germinal center large B-cell lymphoma.

can lead to perforation.[20]

In addition to forming tumor masses, neoplastic lymphoid cells infiltrate in an interstitial pattern, altering the usual histological architecture with separation and loss of normal specialized structures such as glands and intestinal crypts, and sometimes reach the epithelium where they generate ulceration.

Cytologically, DLBCL presents lymphoid cells of large to intermediate size, with morphological characteristics of centroblasts, immunoblasts or intermediate type.[21]

The immunophenotype of DLBCL is determined by the expression of CD45 and Pan-B cell markers such as CD20, CD22, CD79a and PAX5. The other markers present a heterogeneous reactivity with variability in their expression. For example, CD10 is expressed between 25 and 50%, BCL6 between 50 and 90%, BCL2 close to 50%, and MUM1 between 35 and 65%. Ki-67 expression is highly variable, ranging from 30 to 95%.[22]

There are algorithms for immunohistochemical discrimination between germinal center B cells (GCB), as in the second clinical case, and non-germinal activated center B cells (non-GCB), as in the first case. One of the most commonly used is Hans algorithm, which uses CD10, BCL6 and MUM1 markers, considering positive if the expression is present in more than 30% of the tumor cells. With CD10+ or CD10-/BCL6+/MUM1- they indicate a GCB phenotype and with CD10-/BCL6- or CD10-/BCL6+/MUM1+ a non-GCB phenotype.[23]

Intestinal DLBCL is genetically heterogeneous, some with the presence of translocation t (14,18) involving the IGH and BCL2 genes. Other alterations that can be found are t (8,14), involving the IGH and C-MYC genes, t (11,18), involving the API2 and MALT1 genes, and BCL6 abnormalities (Fig. 3).[20]

Treatment

It is necessary to differentiate two scenarios of clinical presentation, urgent and non-urgent. In the first, as in the first case presented, patients consult with symptoms of intestinal obstruction, bleeding that causes anemia, or acute abdomen. In these cases, surgical management will be the initial option, seeking complete resection of the lesion with intestinal anastomosis when feasible, with intestinal diversion being a valid option.[24] The open approach is recommended, unless there is sufficient experience to perform a laparoscopic or video-assisted approach, which according to recent reports is technically possible, does not differ in morbidity and mortality from open surgery, and has faster recovery and shorter hospital stay.[24]

In the non-urgent setting, the treatment of colonic lymphomas, especially the role of surgical management, generates great controversy among experts.[25] There are several studies that have suggested the benefit of surgical management over medical management, with greater evidence in the early stages of the disease, in diffuse B-cell lymphoma and in tumors of the right colon.[18,26]

The rate of complications reported with surgical management or chemotherapy ranges between 20 and 23 % for both.[26] Regarding postoperative complications, most are classified in grades I-III of the Clavien-Dindo classification, with low rates of early postoperative mortality and 16% hospital readmissions at 30 days.[5] The analysis of the "University HealthSystem Consortium Clinical Database/Resource Manager (UHC CDB/RM)" database showed a statistically significant lower rate of complications of right colon resections compared to left colon resections (26.8 vs. 28.3%, $p < 0.05$).[27]

With the exclusive management of chemotherapy, com-

plications have been described mainly in mass-forming tumors of the right colon, with intestinal perforation reported in up to 6%, as well as sepsis associated with chemotherapy, which becomes the cause of mortality in up to 20% of patients who die from this pathology.[5]

The best long-term survival results have been found with the combination of surgical management followed by chemotherapy. The main risk factor for relapse and mortality is the presence of lymph node involvement at the time of diagnosis, with 5-year survival of up to 88-93%.[28]

A retrospective study conducted in Taiwan with 29 patients, compared chemotherapy with surgical management followed by chemotherapy, finding a statistically significant higher overall survival at 3 and 5 years with combined therapy.[29]

Although the role of surgical management in PCL waits to be fully clarified, depending mainly on histology, staging and tumor location, the initial surgical management is accepted by a large number of experts. This is because it provides important prognostic information (including tumor histology, extent, and stage), offers a chance of cure with or without adjuvant therapy, and prevents complications such as bleeding, obstruction, or perforation.[2] Surgical management as immunotherapy could be consider in early stages of the indolent variables of lymphomas, such as MALT and low-grade follicular variants. However, for aggressive variants it is necessary to complete the treatment with adjuvant chemotherapy.[5,29,30]

For aggressive and rapidly proliferating tumors that escape surgical management, primary chemotherapy is recommended.[29] The R CHOP regimen has been preferred for moderate and high-grade B-cell lymphomas due to its benefits comparing to chemotherapy regimens without monoclonal antibodies in terms of higher response rates and higher disease-free and overall survival, even for the older population.[24,29,30]

CONCLUSIONS

PCL is a rare entity that requires a multidisciplinary approach. Two clinical cases of DLBCL are presented, one with a germinal center, with symptoms of slow evolution, which allowed a scheduled surgical resection and the other with a non-germinal center, with less time of symptoms, which required emergency surgery.

In patients in whom this pathology is suspected and do not present an acute abdomen, the initial study should include an abdominal tomography with contrast, followed by a colonoscopy with biopsies.

Once the diagnosis is confirmed, except in low-grade lymphomas, it is recommended to perform a PET-CT for tumor staging and, subsequently, if the patient's conditions allow it, a combined therapy with surgery and postoperative chemotherapy.

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COMMENT

The study presented is of interest given the infrequent presentation of primary colonic lymphoma. The authors describe the clinical presentation, the diagnostic approach, and the surgical resolution of two cases without further information about their oncological evolution. A point to be highlighted, as the authors point out, is the value of immunohistochemistry in the differential diagnosis with other colorectal neoplasms, in many cases indistinguishable in their clinical presentation. This study defines the subsequent adjuvant treatment and the prognosis of the patients. The literature review is complete and is presented in a neat and up-to-date manner, covering the different aspects of a rare disease.

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