Received: 16 November 2022 | Revised: 4 April 2023 | Accepted: 5 May 2023

DOI: 10.1002/ccr3.7381

CASE REPORT

Clinical Case Reports Open Access WILEY

Primary colonic MALT lymphoma associated with Crohn's disease: Case report and review of the literature

Amira Hmidi[1] | **Linda Bel Hadj Kacem**[1] | **Rym Sellami**[2] | **Meriema Ksentini**[1] | **Nadia Znaidi**[1]

[1]Department of Pathology, Hospital Charles Nicolle, Tunis, Tunisia

[2]Department of Pathology, Regional Hospital of Zaghouan, Zaghouan, Tunisia

Correspondence
Amira Hmidi, Department of Pathology, Hospital Charles Nicolle, 138 Boulevard 9 Avril 1938, 1006 Tunis, Tunisia.
Email: hmidiamira.tn@gmail.com

Key Clinical Message

To date, the pathogenic mechanisms of the association between Crohn's disease and MALT lymphoma are ambiguous and yet remain to be elucidated. The publication of other cases illustrating this rare association would be interesting to properly plan therapeutic strategies and to better understand the pathogenesis and the prognosis of this association.

Abstract

Crohn's disease is a progressive disease, with increasing incidence, that leads to bowel damage and disability. Primary colonic MALT lymphoma is a low-grade B lymphoma, representing only 2.5% of all MALT lymphomas. The pathogenesis of these two cancers is still not clearly elucidated and their association is rare. To our knowledge, only two cases have illustrated synchronous Crohn's disease and MALT lymphoma. The possible role of Crohn's disease as a precursor of MALT lymphoma is still debated; some studies proposed that immunosuppressive drugs used in Crohn's disease are involved in the lymphomagenesis of MALT lymphoma. Other studies supposed no relation between these two neoplasms.

We present a rare case of association between Crohn's disease and primary colonic MALT lymphoma in an elderly female patient who had not received any immunosuppressive therapy. The patient presented with chronic diarrhea, epigastric pain, and weight loss. A colonoscopy with biopsies was performed. The histopathologic examination concluded with the diagnosis of not only Crohn's disease but also MALT lymphoma. This discovery of MALT lymphoma was incidental. We highlight the clinical and histopathological features, and we discuss the association between Crohn's disease and MALT lymphoma, which may provide additional information about pathogenic mechanisms.

KEYWORDS

association, case report, chronic inflammatory bowel disease, colon, Crohn's disease, MALT lymphoma

1 | INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease of uncertain etiology. The prevalence of CD is increasing worldwide, predominantly in developed countries, with the highest prevalence in Europe (322 per 100,000), followed by Canada (319 per 100,000), then the USA (214 per 100,000).[1]

Although there is an available fact that patients with chronic inflammatory bowel disease are at increased risk of colorectal carcinoma, the risk of MALT lymphoma is not as well established. The possible role of CD as a precursor of MALT lymphoma is still debated. The association between CD and MALT lymphoma is rare. To our knowledge, only two cases were reported in the literature.[2,3] This type of association has gained widespread interest due to its uniqueness, especially its controversial interference with immunosuppressive therapy and autoimmune conditions. The pathogenic mechanisms, diagnostic strategy, and prognosis of these neoplasms are ambiguous. So, we consider it interesting to present a rare case of primary colonic MALT lymphoma in an 82-year-old female patient with CD who had not received any immunosuppressive therapy.

2 | CASE PRESENTATION

We report a case of an 82-year-old woman with a medical history of CD who presented with chronic diarrhea and epigastric pain in a weight-loss context. The patient seemed poorly controlled and had not received any therapy for her disease. On examination, she weighed 38 kg. Her pulse rate was 90 beats per minute and her blood pressure was 105/60 mmHg. She had not any signs of dehydration or fever. On abdominal examination, no abnormalities were detected on inspection, peristalsis bowel sounds were normal, and palpation showed deep tenderness without mass. Rectal examination was normal.

Laboratory tests at presentation showed anemia (hemoglobin 8.3 g/dL), an elevated leucocyte level of 13,000/mm^3, and increased acute phase protein (C-reactive protein 39 mg/L).

An abdominal CT revealed wall thickening of the colon and several enlarged mesenteric lymph nodes with a diameter ranging from 10 to 21 mm. Endoscopy demonstrated a congestive antral gastropathy.

Colonoscopy showed segmental inflammation, congested mucosa of the right colon dotted with multiple superficial ulcers (Figure 1A), a suspicious depressed lesion, and a polypoid tumor in the right angle (Figure 1B).

The rectum and the sigmoid colon were normal.

The histological examination of gastric biopsies showed chronic active *Helicobacter pylori* pangastritis with no atrophy nor intestinal metaplasia. Polyp biopsies showed an inflammatory pseudo polyp without signs of malignancy. The histological examination of the depressed lesion showed histological features of CD with architectural distortion (Figure 2A), basal plasmacytosis, cryptitis, and epithelioid and gigantocellular granuloma (Figure 2B).

Multiple biopsies of the ulcerated mucosa showed a dense diffuse and nodular lymphoid infiltrate of small lymphocytes that invade glands and result in the so-called "lymphoepithelial lesion" (Figure 3). Small lymphocytes showed positivity for CD20 and BCL2, and negativity for CD3 and CD5 (Figure 4).

Based on morphological and phenotypic features, the diagnosis of primary colonic MALT lymphoma associated with Crohn's disease and chronic *Helicobacter pylori* pangastritis was retained. The association between CD and MALT lymphoma, as well as, the possible role of HP will be discussed later. *Helicobacter pylori* eradication therapy was prescribed.

The patient has been scheduled for surgical treatment, but he was lost to follow-up.

3 | DISCUSSION

CD is a chronic inflammatory bowel disease with increasing incidence worldwide.[1] Its etiology is still unclear, resulting from a complex interference of genetic

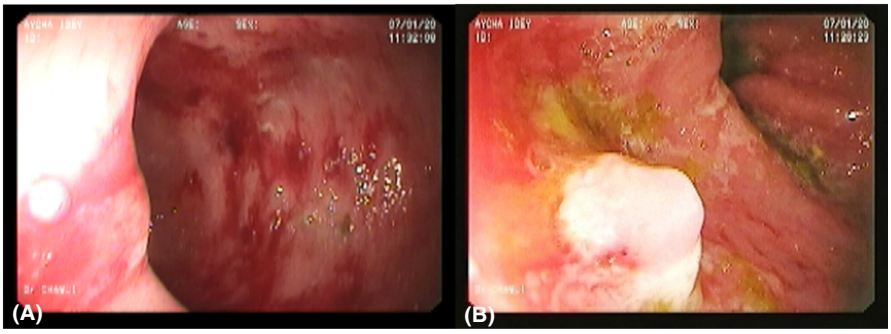


FIGURE 1 Colonoscopy shown in (A) multiple superficial ulcers and in (B) a sessile polypoid mass.

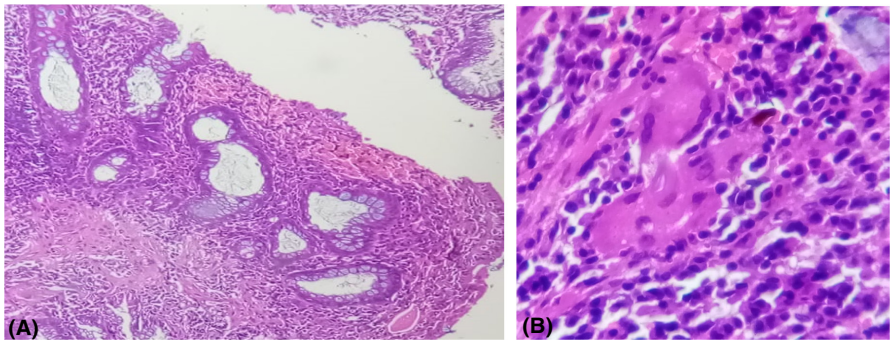
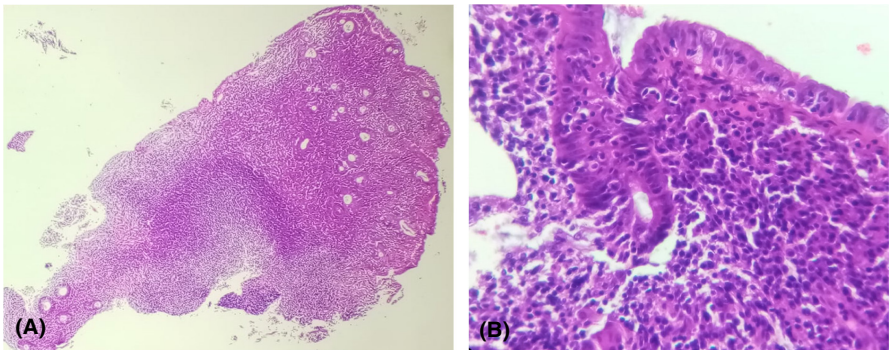


FIGURE 2 Crohn's disease. (A) Distortion of the mucosal architecture: showing bifid crypts characterized by the presence of double lumina (*) (H&E ×100). (B) Epithelioid cell granuloma is accompanied by multinucleated giant cells forming the so-called epithelioid and gigantocellular granuloma (H&E ×400).

FIGURE 3 MALT lymphoma: (A) Colonic biopsy showing colonic mucosal expansion by diffuse and nodular infiltrate of small lymphoid cells. There is destruction of the architecture with loss of glands (H&E ×20). (B) This magnification view shows infiltration of the epithelium by small lymphocytes: lymphoepithelial lesion (H&E ×400).



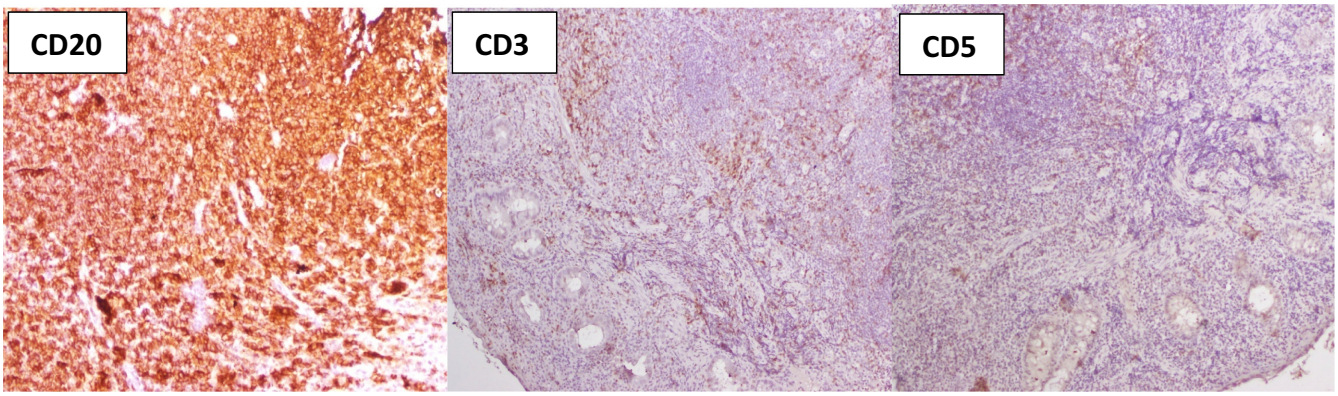


FIGURE 4 Immunohistochemistry staining: small lymphocytes are strongly stained with CD20 and showed negativity for CD3 and CD5. Note that some mature T-cells in the background are stained with CD3 and CD5.

predisposition, environmental factors, and intestinal microbiota, leading to a disorder in the mucosal immune response.[1]

CD is characterized by recurrent episodes of mucosal inflammation. This chronic mucosal inflammation increases, significantly, the occurrence of dysplasia and colorectal neoplasia. Dysplasia in CD is distributed more evenly throughout the colon and is present adjacent to cancer in more than 80% of cases.[4] Epidemiologic studies continue to highlight the increased risk of colorectal cancer in inflammatory bowel disease with an estimated incidence of nearly 1% per year.[5] This incidence can vary, considerably, over-time and across populations.[5] The risk of colorectal cancer in inflammatory bowel disease increases with the extension and the duration of the disease, with an incidence of 1%, 2%, and 5% after 10, 20, and > 20 years of disease duration.[6]

Patients with CD are also at increased risk of developing lymphoma. This risk is controversial; some studies approved that CD can, significantly, increase the risk of extranodal lymphomas,[7,8] others revealed no increase in lymphoma risk in patients with CD.[9,10] Several types

of lymphoma have been described in patients with CD: Hodgkin's lymphoma, follicular lymphoma, anaplastic large cell lymphoma, Hepato-splenic T-cell lymphoma, EBV-associated plasmablastic lymphoma,[2] and MALT lymphoma.[2,3]

Extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma), as defined recently by the World Health Organization[11] is a unique type of lymphoma different from other extranodal lymphomas.

MALT lymphoma was first described by pathologists Peter Isaacson and Dennis Wright in 1983,[12] forming the basis for the current definition of MALT lymphoma, which is a diagnosis based on pathological features characterized by a dense lymphoid infiltration that invades and destroys glands and results in the so-called "lymphoepithelial lesion" which is pathognomonic for MALT lymphoma. They have a particular predilection for the gastrointestinal tract with the stomach being the most common site.[11]

MALT lymphoma occurs rarely within the colon. It has been reported that only 2.5% of all MALT lymphomas originate from the colon.[13] In our case, MALT lymphoma was localized in the right colon. A few cases series of colonic MALT lymphoma were reported in the literature.[13–16] The mean age of colonic MALT lymphoma is 60 years old with no sex predilection. MALT lymphoma of the colon is often asymptomatic and is discovered incidentally.[14] However, variable clinical presentations were reported: chronic epigastric pain, weight loss, fatigue, change in transit, and nausea. In the present case, the patient presented with diarrhea and epigastric pain.[13,15,16]

The endoscopic appearance of colonic MALT lymphoma can include multiple ulcerations, as in the case presented here, or polypoid lesions, obstructive tumors, flat lesions, and vascular telangiectasia.[13–16] The lesion may be solitary or multiple.

To the best of our knowledge, only two cases of intestinal MALT lymphoma in patients with CD were reported[2,3] (Table 1).

The association between CD and MALT lymphoma is controversial. Several etiologic factors have been postulated to explain this rare association, such as immunosuppressive drugs and immune disorders in inflammatory bowel disease.

Some studies proposed that immunosuppressive drugs used in inflammatory bowel disease (azathioprine, methotrexate, and infliximab) are involved in the lymphomagenesis of MALT lymphoma.[8] Infliximab is a medication used to treat several autoimmune diseases, including inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Behcet's disease. In the case of inflammatory bowel disease, excessive production of a protein called tumor necrosis factor-alpha (TNF-alpha) can lead to inflammation that damages tissues. Infliximab works by blocking the action of TNF-alpha which suppresses the immune system, reduces inflammation, and leads to the appearance of lymphomatous proliferation.[8] In our case, the patient seemed poorly controlled and had not received any immunosuppressive therapy for her disease. Other studies explain the association between CD and MALT lymphoma by the abnormal activation of the immune system in CD leading to disorder in the mucosal immune response which promotes lymphomatous proliferation. This immune disorder increases the risk of developing lymphomas, especially, large B-cell lymphoma and marginal zone lymphoma.[17] However, this association may not be general.

Other studies suppose that there is no relation between CD and MALT lymphoma and suggest that the occurrence of a lymphoma in the context of CD can be related to chronic infections such as *Helicobacter pylori* (HP). Indeed, the translocated HP cytotoxin-associated gene A

TABLE 1 Reported cases of intestinal MALT lymphoma in patients with CD.

Case	Age (years)	Sex	IS	Symptoms	Colonoscopy	Location of MALT.L	Interval (years)	Follow-up
García-Sánchez, 2006[3]	79	F	No	Diffuse abdominal pain, diarrhea, anorexia, weight loss	Neoformation covered with erythematous mucosa, ulcers	Right colon	3	The patient received chemotherapy
Bennani et al, 2019[2]	50	M	No	Weight loss, diarrhea alternating with constipation	Many discontinuous ulcerations with a sessile polypoid mass	Ileum	0[a]	The patient underwent ileocolectomy with no recurrence 10 months after surgery

Abbreviations: F, female; IS, immunosuppressive drugs; Interval, interval between the diagnosis of CD and MALT.L; M, male; MALT.L, MALT lymphoma.

[a]CD and MALT lymphoma was diagnosed synchronously in the same surgical specimen.

(Cag A) and Cag A-signaling molecules can promote B-cell proliferation.[18] HP has an important role in the pathogenesis of gastric MALT lymphoma, but this is not well defined in the colon. A published study by Keenan et al in 2010 revealed the DNA of Helicobacter species in colon biopsies.[19] This study confirmed that the colon can be colonized by Helicobacter species but suggested no specific relation between this micro-organism and colon disease. In our case, HP was found in the stomach but colonization patterns of HP throughout the colon have not been searched. Thus, the incrimination of HP in the occurrence of MALT lymphoma, with concomitant CD is less likely but still possible.

Owing to the lack of a definite pathogeny and the small number of reported cases, there is currently no consensus regarding the treatment of concomitant CD and MALT lymphoma. In the absence of a standardized treatment, various methods have been used, including surgery, chemotherapy, and radiation. For low-grade MALT-lymphoma, surgical treatment with tumor resection and systematic lymphadenectomy can be sufficient. However, in high-grade cases, the treatment of choice could be CHOP chemotherapy (cyclophosphamide, adriamycin, vincristine, and prednisone).[20] In our case, given the patient's age and the possibility of more significant side effects related to chemotherapy, surgical treatment was chosen.

The prognosis of colonic MALT lymphoma is worse than colorectal adenocarcinoma, although its metastatic potential is not completely known.[21] However, as we do not have enough data, we are not sure if the association with CD worsens the prognosis.

4 | CONCLUSION

We presented the case of an 82-year-old female patient with untreated CD, who was incidentally diagnosed with primary colonic MALT lymphoma. This case underlines the possibility of the association between CD and MALT Lymphoma. This association can provide additional information about pathogenic mechanisms.

Some studies support the association between CD and MALT Lymphoma and explain this association through the use of immunosuppressive drugs in CD which can suppress the immune system.

To date, the pathogenic mechanisms of the association between CD and MALT lymphoma are ambiguous and yet remain to be elucidated. The publication of other cases illustrating this rare association would be interesting to properly plan therapeutic strategies and to better understand the pathogenesis and the prognosis of this association.

AUTHOR CONTRIBUTIONS

Amira Hmidi: Conceptualization; funding acquisition; investigation; methodology; writing – original draft; writing – review and editing. **Linda Bel Hadj Kacem:** Conceptualization; data curation; funding acquisition; methodology; resources. **Rym Sellami:** Funding acquisition; project administration; resources; visualization. **Meriem Ksentini:** Formal analysis; software; supervision.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Amira Hmidi https://orcid.org/0000-0002-5386-8140

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How to cite this article: Hmidi A, Bel Hadj Kacem L, Sellami R, Ksentini M, Znaidi N. Primary colonic MALT lymphoma associated with Crohn's disease: Case report and review of the literature. *Clin Case Rep*. 2023;11:e7381. doi:10.1002/ccr3.7381