

The Pillow Sign: Is It Always Benign?

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ABSTRACT

Mucosa-associated lymphoid tissue (MALT) lymphoma is classically found in the stomach; however, in less common, cases can be found in extragastric locations. Colonic MALTomas are exceedingly rare and comprise a small group of extragastric cases. There is no standardized approach for optimal management of this disease. We report a case of a colonic MALT lymphoma found on colonoscopy that demonstrated the pillow sign and appearance of a benign lipoma. Despite antimicrobial and endoscopic therapy, the malignancy reoccurred in a patient with chronic hepatitis B, thereby precluding one of the mainstays of treatment, rituximab, until viral eradication.

INTRODUCTION

Extranodal marginal zone lymphoma, also known as low-grade B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), is an indolent form of non-Hodgkin lymphoma that comprises approximately 5%-10% of all non-Hodgkin lymphoma.^{1,2} These lymphomas tend to occur in the setting of chronic immune activation, including autoimmune or infectious etiologies such as Sjogren, systemic lupus erythematosus, *Helicobacter pylori*, *Campylobacter jejuni*, hepatitis B (HBV), and hepatitis C (HCV).^{3,4} MALT lymphomas classically originate in the stomach, with less common occurrences in extragastric locations. Primary extranodal marginal zone lymphoma of the large intestine occurs infrequently.² As a result, there is no standardized approach for the treatment of colonic MALT lymphomas when compared with their gastric counterparts.^{2,5} We report a case of a colonic MALT lymphoma incidentally found on biopsy obtained during colonoscopy and the complexity of treatment in the setting of chronic HBV.

CASE REPORT

A 56-year-old man from China with a history of untreated chronic HBV (HBV surface antigen-positive, HBV e-antigen negative, HBV e-antibody positive, and HBV viral load of 1007 IU/mL) with negative HCV and human immunodeficiency virus serology presented to his primary care physician with 1 month of unintentional 10-pound weight loss and worsening fatigue. He denied abdominal pain, nausea, vomiting, diarrhea, constipation, hematochezia, melena, night sweats, or fevers. There was no family history of gastrointestinal malignancy. He had a 30 pack-year smoking history and consumed several beers per day. Liver function tests were notable for aspartate aminotransferase 44 IU/L, alanine aminotransferase 50 IU/L, alkaline phosphatase 88 IU/L, lactate dehydrogenase 368 IU/L, and total bilirubin 0.8 mg/dL. An abdominal ultrasound revealed cholelithiasis.

A colonoscopic evaluation revealed a 6-mm subepithelial lesion at the hepatic flexure with a positive pillow sign (Figure 1). Biopsies of the lesion were obtained by tunnel biopsy with jumbo cold forceps, which returned diagnostic for extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue with immunochemical staining positive for PAX5, CD20, CD43, BCL2, and MUM1 while negative for CD5, CD10, CD23, BCL6, CD30, and Cyclin D1 (Figure 2). Esophagogastroduodenoscopy was grossly unrevealing; however, biopsies of the antrum and body returned positive for *H. pylori*-associated chronic active gastritis without dysplasia. *H. pylori* stool antigen was also positive, and the patient was treated with clarithromycin, amoxicillin, and omeprazole with eradication of *H. pylori* confirmed

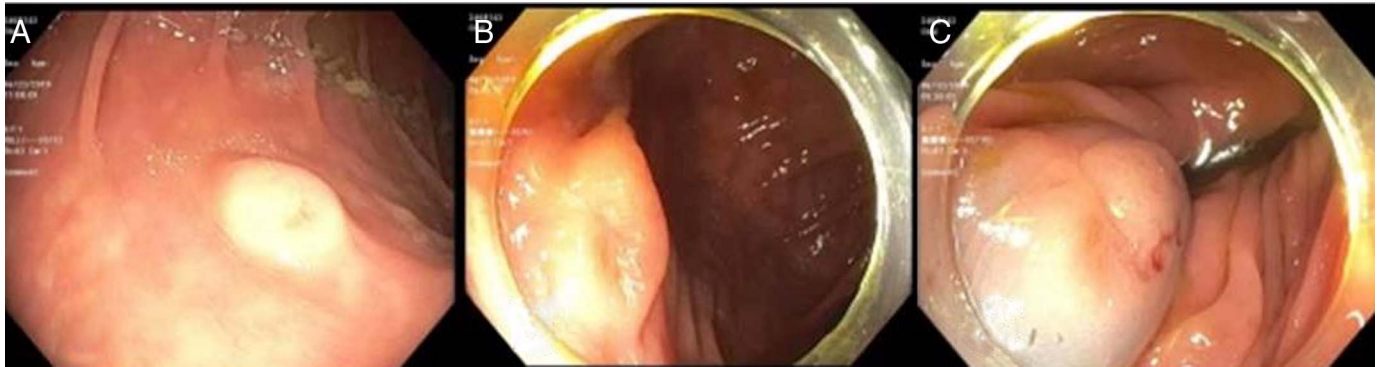


Figure 1. The 6-mm subepithelial lesion exhibiting the pillow sign at the hepatic flexure shows (A) the original lesion at hepatic flexure before intervention, (B) a closed forceps-induced indentation, and (C) reversion of the indentation with the lesion returning to its original shape.

through negative stool antigen. Thoracic, abdominal, and pelvic computed tomography for staging did not demonstrate metastatic lesions. Positron emission tomography scan showed reactive cervical lymph nodes but no metastatic disease.

After a multidisciplinary discussion, the decision was made to proceed with endoscopic mucosal resection given the lack of metastatic disease and the desire to avoid rituximab in the setting of chronic HBV. The patient underwent a repeat colonoscopy with en bloc injection-assisted endoscopic mucosal resection of the colonic MALT lymphoma. The resection edge was treated with snare tip soft coagulation current to decrease the risk of recurrence and closed with hemostatic clips. Surveillance colonoscopy 6 months later showed no obvious recurrence, but biopsies of the mucosectomy scar were diagnostic of persistent MALT lymphoma (Figure 3). As a result, he is currently undergoing further evaluation of treatment for his chronic HBV for possible initiation of rituximab.

DISCUSSION

The endoscopic pillow sign refers to the creation of a surface indentation made by pressing the tip of a cold forceps onto a subepithelial lesion.⁶ In most cases, the pillow sign has been associated with benign lipomas.⁷ It is argued that conventional biopsies of these lesions are of little utility because they are superficial, limited to the surface mucosa, and rarely diagnostic.⁶ Therefore, most of these

lesions are not biopsied and managed expectantly.⁸ Although colonic MALT lymphomas are rare, this is the first case to the best of our knowledge presenting as a lesion exhibiting the pillow sign.

The management of colonic MALT lymphoma is highly debated. Because of the low incidence of the disease, a standardized approach has been difficult to establish. Management ranges from *H. pylori* eradication, chemotherapy, radiotherapy, immune therapy with rituximab, endoscopic mucosal resection, and/or surgery.⁸ Eradication therapy for *H. pylori* has had variable outcomes for colonic MALT lymphomas. There is less correlation between *H. pylori* and primary colonic MALT lymphomas, when compared with gastric MALT lymphomas. A limited number of case reports have demonstrated colonic MALT lymphoma regression with *H. pylori* eradication treatment.^{5,8} However, several studies suggest that *H. pylori* treatment is ineffective in nongastric MALT lymphomas with such patients often resorting to surgery or chemotherapy.^{2,9,10}

Radiotherapy has become less appealing for treating colonic MALT lymphoma because of potential adverse intestinal effects.¹¹ The mainstay of chemotherapy consists of alkylating agents.¹¹ In retrospective studies, recurrence has been low for patients who underwent chemotherapy alone.¹² Because of toxicities associated with chemotherapy, it is commonly used for patients with extensive disease. More recently, immune therapy with rituximab has been used with some success and

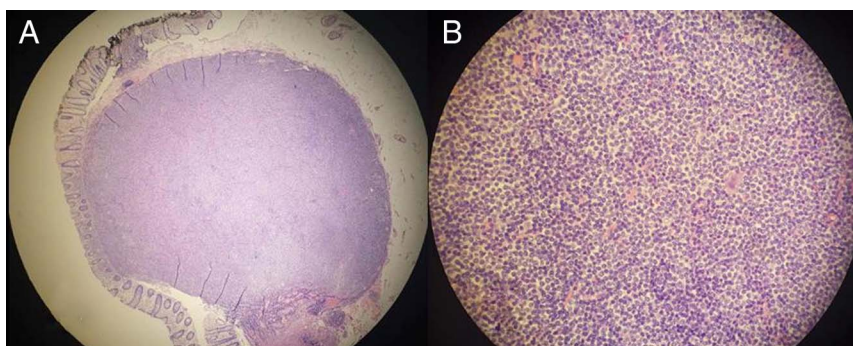


Figure 2. Pathology of hepatic flexure lesion under (A) low power and (B) high power in the colonic submucosa comprised atypical small- to medium-sized B lymphocytes which is diagnostic for mucosa-associated lymphoid tissue lymphoma.

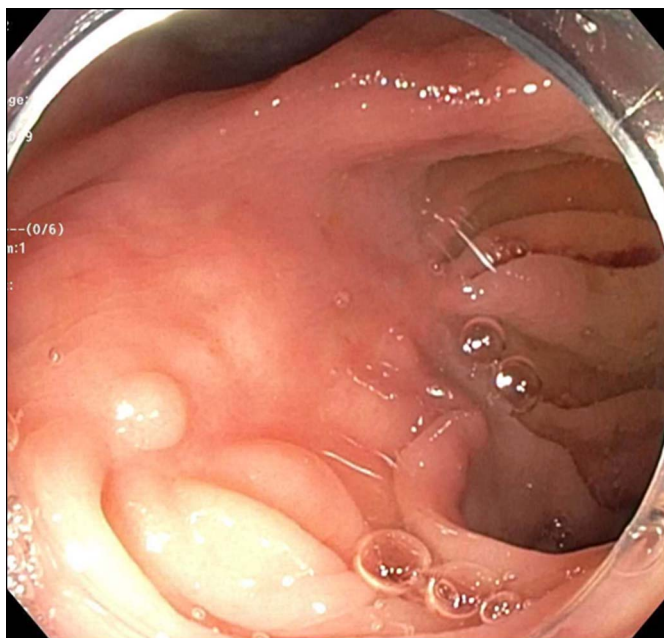


Figure 3. The postmucosectomy scar found at the hepatic flexure.

demonstrates a favorable side-effect profile when compared with most alkylating agents.^{2,13} However, rituximab alone, without endoscopic or surgical resection, has been unsuccessful in achieving remission in limited cases.¹³ In addition, immune therapy increases the reactivation risk of chronic viral and bacterial conditions and should be used with caution in this setting, as with the case presented.

Endoscopic and surgical resection provide more definitive treatment options.¹⁰ Most reported cases of colonic MALT lymphoma document localized disease, as opposed to metastatic disease, at the time of diagnosis. Many reports demonstrate no recurrence after endoscopic or surgical resection.^{10,14} There have been no prospective studies comparing recurrence after endoscopic vs surgical resection, likely because of the limited case numbers. Endoscopic ultrasound, which can evaluate for signs of invasion, may be of benefit in deciding which initial intervention to pursue.^{15,16}

This case describes an unusual presentation of a rare entity, colonic MALT lymphoma, and highlights the complexities of treating this disease. The differential diagnosis for lesions exhibiting the pillow sign should not be limited to benign etiologies alone. Colonic MALT lymphoma should be considered as well. In our case, despite *H. pylori* eradication and endoscopic mucosal resection, disease recurrence occurred. Many questions remain unanswered concerning colonic MALT lymphoma, and more research is needed to devise a treatment algorithm that can assist with maintaining remission.

DISCLOSURES

Author contributions: All authors contributed equally to this manuscript. S. Alvencar is the article guarantor.

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