Helicobacter pylori–negative gastric mucosa–associated lymphoid tissue lymphoma: magnifying endoscopy findings

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A B S T R A C T

Gastric mucosa–associated lymphoid tissue lymphoma is uncommon and most patients have an indolent clinical course. The clinical presentation and endoscopic findings can be subtle and diagnosis can be missed on white light endoscopy. Magnifying endoscopy may help identify the abnormal microstructural and microvascular patterns, and target biopsies can be performed. We describe herein the case of a 64-year-old woman with *Helicobacter pylori*–negative gastric mucosa–associated lymphoid tissue lymphoma diagnosed by screening magnification endoscopy. *Helicobacter pylori*–eradication therapy was given and she received biological therapy. She is in clinical remission after treatment. The use of magnification endoscopy in gastric mucosa–associated lymphoid tissue lymphoma and its management are reviewed.

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Introduction

Primary extranodal low-grade B cell lymphoma of the mucosa-associated lymphoid tissue (MALToma) of stomach is uncommon. The clinical presentation is variable and there is no endoscopic hallmark. Magnifying endoscopy (ME) may help in the diagnosis of gastric MALToma. Herein we report the case of a patient who had gastric MALToma diagnosed by ME.

Case report

A 64-year-old woman had a history of cancer of alveolus that was in remission. She was considered at increased risk of developing squamous cell carcinoma of the upper aero-digestive tract; therefore, she was referred to us for endoscopic screening in May 2012. On white light endoscopy, a well-demarcated erythematous zone measuring 3 cm in size was identified at the distal greater curvature of the stomach (Fig 1a). To further delineate this suspicious lesion, ME combined with narrow-band imaging (NBI) was used. Magnifying endoscopy was performed with a zoom endoscope (GIF-Q260Z; Olympus Hong Kong and China Ltd, China) which has a magnifying power of 80 times. The tip of the endoscope was mounted with a transparent cap for the purpose of focusing. Under ME in combination with NBI, a non-structural area, ie, complete or almost-complete disappearance of gastric crypt epithelium and abnormal mucosal capillary pattern was identified (Fig 1a). Biopsy of the suspicious zone revealed atypical lymphoid cells with lymphoepithelial lesion formation. Immunohistochemical stains confirmed that the atypical lymphoid cells were positive for B cell marker CD20 (pan-B-cell marker: L26, Dako, UK), and negative for T cell markers CD3 and CD5 (Fig 2). *Helicobacter pylori* was not found. These findings were consistent with gastric MALToma. Whole-body positron-emission tomography scan did not show abnormal uptake in the stomach and the rest of body.

The patient was empirically treated with *H pylori*–eradication therapy (esomeprazole 20 mg twice daily, amoxicillin 1 g twice daily, and clarithromycin 500 mg twice daily for 1 week). She was then treated with four doses of rituximab (weekly for 4 weeks); this treatment was completed in June 2012. Repeated endoscopy and biopsy at 4 weeks after treatment showed a residual focus of MALToma. Radiotherapy (30 Gy) was subsequently given for improved local control in view of partial response to rituximab, which was completed in December 2012. Endoscopy performed 6 weeks after completion of radiotherapy showed complete response, ie, recovery of gastric pit pattern under ME (Fig 1b).

Discussion

Gastric MALToma is uncommon and accounts

幽門螺桿菌陰性胃黏膜相關淋巴組織淋巴瘤：放大內鏡的結果

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胃黏膜相關淋巴組織淋巴瘤（MALToma）不常見，大多數患者的臨床過程緩慢，其臨床表現和內鏡檢查結果亦很細微，普通白光內鏡檢查很可能會錯過細微的胃黏膜異常病變。放大內鏡可幫助識別異常的微觀結構和微血管形態，從而進行目標活檢。本文描述一名64歲女性，經放大內鏡檢查後證實患有幽門螺桿菌陰性的MALToma。為患者根除幽門螺桿菌並進行生物治療後見臨床緩解。本文綜述放大內鏡對診斷MALToma的作用及MALToma的治療方法。

for 1% to 5% of all gastric cancers. Isaacson and Wright[1] first reported a low-grade gastric lymphoma in 1983. Lymphoid tissue is absent in the normal gastric mucosa. *Helicobacter pylori* is believed to play a causative role in the development of gastric MALToma.[2] Gastric lymphoid tissue is acquired in response to local infection by *H pylori*, and there is a strong association between *H pylori* infection and gastric MALToma. Approximately 90% of gastric MALTomas are *H pylori* positive. Pathogenesis of gastric MALToma is a multistep process; *H pylori* infection causes chronic gastritis, which leads to immunological reaction with formation of lymphoid follicles and, subsequently, to genetic abnormalities and malignant transformation. Eradication of *H pylori* may lead to remission in 50% to 90% of cases.[3,4] Most patients with gastric MALToma have an indolent clinical course; the 5-year overall survival after *H pylori* eradication has been reported to be 82% to 96%.[5,6]

The presentation of MALToma is variable. Patients may present with non-specific symptoms such as epigastric pain, vomiting, and weight loss. Endoscopy with biopsy is diagnostic but there is no endoscopic hallmark. The endoscopic appearance is also non-specific. It is difficult to differentiate gastric MALToma from gastric erosion or gastritis on conventional white light endoscopy. Diagnosis can be easily missed if multiple biopsies are not taken. Narrow-band imaging allows enhanced visualisation

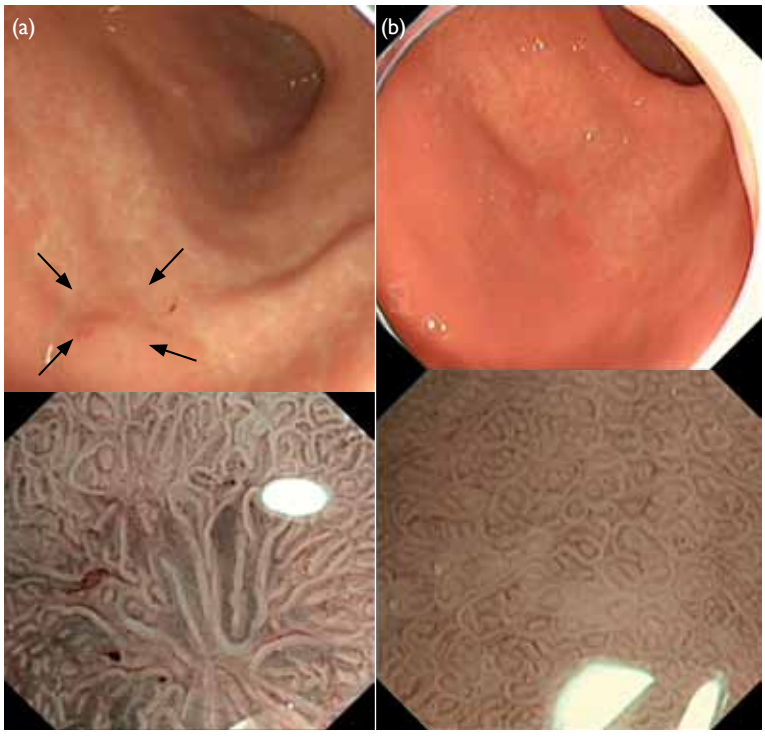

FIG 1. White light endoscopic images (upper) and magnified endoscopic images (lower)
(a) Magnified endoscopic image before treatment showing disappearance of the normal gastric pit pattern and appearance of irregular abnormal vessels (arrows). (b) Magnified endoscopic image after treatment showing recovery of gastric pits

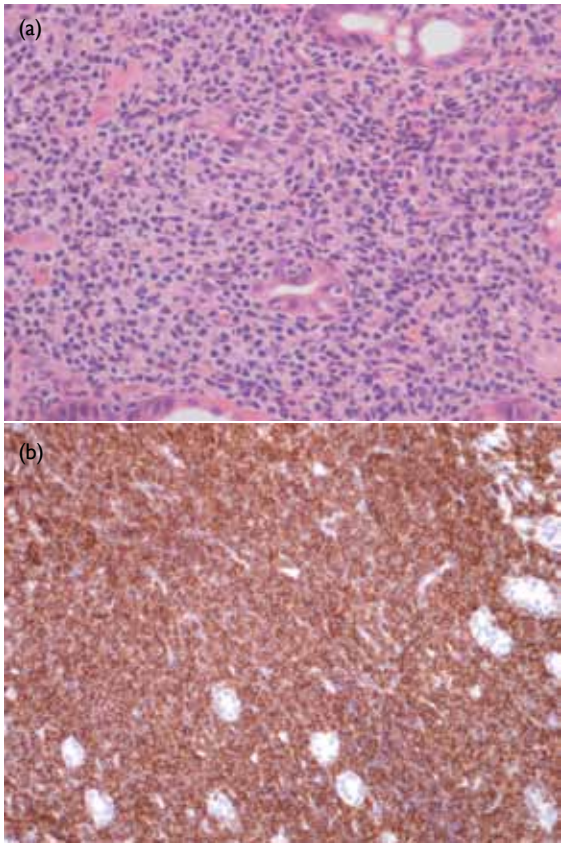

FIG 2. Histopathology before treatment
(a) The atypical lymphoid cells form lymphoepithelial lesions. They show pale cytoplasm and mildly irregular hyperchromatic nuclei (H&E; original magnification, x 40). (b) The atypical lymphoid cells are diffusely positive for B cell marker CD20

of microvascular and microsurface structures in the superficial part of the mucosa. The use of ME with NBI is useful for the diagnosis of early gastric cancer.[7] Recently, retrospective studies have shown the characteristics of gastric MALToma on ME. Chiu et al[8] reported abnormal spider-like vasculature and disappearance of gastric pits in nine patients with histological diagnoses of gastric MALToma, while Ono et al[9] reported that non-structural areas with abnormal vessels were observed in 11 patients before treatment. The use of ME may help the endoscopist to take targeted biopsies from the abnormal areas.[10]

The histological criteria of gastric MALToma were established according to the World Health Organization criteria in 2001, which included (i) invasion of epithelial structures resulting in 'lymphoepithelial lesions'; (ii) small lymphocytes, marginal zone cells, and/or monocytoid B cells; (iii) infiltration of diffuse, perifollicular, interfollicular, or even follicular type due to colonisation of reactive follicles.[11]

Surgery has been replaced by medical therapy in the management of gastric MALToma.[12] It is generally recommended that *H pylori*–eradication therapy be the first-line therapy for *H pylori*–positive patients with localised gastric MALToma; eradication therapy should also be given to *H pylori*–negative patients, as there may be false-negative results.[13] About 60% to 90% of patients with gastric MALToma achieve complete response after *H pylori* eradication.[13] The presence of atrophic-like mucosa is a characteristic finding after treatment of gastric MALToma. Reported post-treatment ME findings include recovery of gastric pits and resolution of abnormal vascular pattern.[8] It was demonstrated that the disappearance of non-structural areas with abnormal vessels was related to pathological remission.[10]

There is no consensus on treatment for those who fail to respond to eradication therapy. It is evident that patients with progressive disease or clinically evident relapse should undergo further treatment. Different treatment modalities include chemotherapy and radiotherapy. In a recently published multicentre cohort, high response rate to radiotherapy (94%) and chemotherapy (88%) was reported when used as second-line treatment in 82 non-responders and eight responders with relapse.[14] Nine patients (out of 420 patients) showed transformation into diffuse large B cell lymphoma at a median follow-up period of 6 years.[14] The management of patients with clinically partial remission is not well defined. A 'watch and wait' strategy has been advocated, and patients are followed up with interval endoscopies for evidence of progressive disease before considering oncological treatment.[14] Rituximab, a chimeric antibody directed against CD20, is another therapeutic option. CD20 is a B cell–specific antigen expressed abundantly by the neoplastic cells of MALToma. The response rate has been reported to be around 70% in small series.[15]

In summary, patients with gastric MALToma present with non-specific symptoms, and there is no endoscopic hallmark. Endoscopy and biopsy are the gold standard for diagnosis. Magnifying endoscopy findings in MALToma include abnormal vessel patterns and disappearance of gastric pits; however, these findings have not been confirmed by large-scale prospective studies. *Helicobacter pylori* eradication is the first-line treatment. While the majority of patients respond to eradication therapy, those who fail to respond and develop progressive disease require oncological treatment. The management of partial responders is uncertain. Surveillance endoscopy is recommended in the follow-up of patients with MALToma in order to detect relapse.

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