Simultaneous Primary Low-Grade Mucosa-Associated Lymphoid Tissue Lymphoma of Stomach and Duodenum

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Dear Sir,

With the introduction of the entity MALT (mucosa-associated lymphoid tissue) lymphoma by Isaacson and Wright, more and more MALT lymphomas have been diagnosed. Most MALT lymphomas arise from gastrointestinal organs as well as from extragastrointestinal organs such as the salivary gland, thyroid gland, lung, bladder, and skin. In the majority of the studies, the stomach is the most common site involved, accounting for more than 75% of gastrointestinal tract lymphomas [1], while simultaneous MALT lymphoma of stomach and duodenum is very rare. To our knowledge, very few cases of primary gastrointestinal lymphoma that involve both stomach and duodenum are reported in the literature. We report here a very rare case with MALT lymphoma arising in both stomach and duodenum and review the literature.

Case Report

A 44-year-old woman was referred to our hospital in February with a 6-month history of intermittent epigastric discomfort and accompanying vomiting, anorexia and weight loss. An initial upper gastrointestinal endoscopy performed by her first practitioner showed no serious lesion aside from slight swelling of the mucosal folds. Meanwhile, a magnetic resonance cholangiopancreatography (MRCP) carried out in a local hospital revealed expansion both within and outside the liver bile duct but found no stone or neoplasm. Then, she was referred to our hospital where physical examination revealed epigastric tenderness while the liver, spleen, and superficial lymph nodes were not palpable. The patient’s main laboratory data showed no abnormality except for a slight elevation of tumor markers CA199 and CA242. The chest X-ray, computed tomography scan of the abdomen and chest X-ray showed no abnormality except for a slight elevation of tumor markers CA199 and CA242. The chest X-ray, computed tomography scan of the abdomen and peripheral blood were normal. On the basis of the above investigations, we planned to perform an ERCP (endoscopic retrograde cholangiopancreatography) to confirm the diagnosis. To our surprise, we observed large hypertrophied rugal folds as well as multiple mucosal ulcerations in both stomach and duodenum (fig. 1a, c). While waiting for the biopsies to be reviewed, a barium examination of the gastrointestinal tract revealed enlarged mucosa folds throughout the whole stomach and a diffuse spread of disease in the whole duodenum (fig. 2). Histologic sections of the biopsies showed mucosal interstitial cells with large stained nucleus (fig. 3a). 14C-Urea breath test showed Helicobacter pylori infection. Repeat multiple deeper biopsies were taken and revealed histopathologic findings consistent with the diagnosis of low-grade MALT lymphoma. Immunohistochemical stains demonstrated the lymphocytes to be CD20, LCA-positive and CD3, CD5, CD10, CK, EMA-negative. On endoscopic ultrasound (EUS), lesions appeared hypoechoic and were limited to the mucosa and submucosa. The muscularis propria was intact and no local lymph node was noted (fig. 1e). No extragastrointestinal involvement was found by clinical examination, computed tomography scan of the abdomen and chest X-ray. The bone marrow biopsy was also normal.

It is reported that 33% gastric lymphoma can spread across the pylorus into the duodenal bulb, while the whole duodenum involvement has not been reported [2]. In our patient, the barium meal showed lesions in the whole duodenum and the MRCP revealed obstruction of common bile duct. Therefore, we believe both the stomach lymphoma and the duodenum lymphoma are primary gastrointestinal lymphomas. And the outlet of common bile duct may also be involved.

As there was so much persuasive evidence that the gastric MALT lymphoma was related to H. pylori, eradication of H. pylori was recommended as the primary choice in the treatment of primary low-grade gastric MALT lymphoma [3]. The patient was treated with a 14-day course of pantoprazole, amoxycillin and clarithromycin, followed by six cycles of CHOP (cyclophosphamide 750 mg/m2 day 1, doxorubicin 50 mg/m2 day 1, vincristine 1.4 mg/m2 day 1, prednisone 50 mg days 1–5, six cycles repeat every 21 days). The patient...
was followed up closely with endoscopies, CT scans and complete blood count and biochemistry in addition to biopsy, but no evidence of tumor deterioration was detected after 6 months (fig. 1b, d, f) and (fig. 3b). Meanwhile, eradication of *H. pylori* was proved successful by a follow-up 14C-urea breath test.

**Discussion**

It is well known that the primary extranodal malignant MALT lymphoma which was first introduced by Isaacson and Wright can arise in a variety of anatomical sites such as the gastrointestinal tract, salivary gland, thyroid gland, lung, breast, bladder, and skin. The stomach is the most commonly involved site, accounting for more than 75% of gastrointestinal tract lymphoma while simultaneous MALT lymphoma of stomach and duodenum is very rare [1]. There were only 3 cases that had been found from 1983 to 2009 in PubMed. These reports were from Italy [4], Japan [5] and Israel [6]. Therefore, the case reported here is a very rare one of this condition.

It has been reported that low-grade gastric MALT lymphoma is a neoplasm with a favorable clinical behavior and an excellent prognosis. However, the early diagnosis of gastric MALT lymphoma is unsatisfactory, because of the very indolent course and various endoscopic patterns. In the past decades, diagnosis of primary gastrointestinal lymphoma by endoscopic evaluation has markedly improved. There were series reporting that successful endoscopic diagnosis of lymphoma was up to 92% while other series reported that a correct diagnosis by endoscopy was from 38 to 92% [7, 8]. When certain findings such as a bulky mass or diffuse infiltration with preservation of fat planes and no obstruction, multiple site involvement were disclosed by endoscopy, we should take lymphoma into consideration. But in the early phases of gastrointestinal MALT lymphoma, the histologic evaluation of endoscopic biopsies including immunohistochemistry represents the diagnostic procedure more reliably to detect the tumor. Once the diagnosis of gastrointestinal MALT lymphoma is established EUS is recommended, which is considered to be a sensitive procedure for initial staging and assessment of treatment response and long-term follow-up in patients with gastrointestinal lymphoma. In our case, multiple mucosal ulcerations and large hypertrophied rugal folds were observed by esophagogastroduodenoscopy.
As we known, H. pylori infection and gastric MALT lymphoma is well established and if only low-grade MALT lymphomas are considered, H. pylori prevalence is high, nearly 90% [9]. Moreover, a high regression of MALT lymphoma following eradication has been reported which highlights the role of H. pylori in gastric MALT lymphoma [10]. Morgner et al. [3] reported that eradication of H. pylori infection is associated with complete remission in approximately 80% of patients with low-grade MALT lymphoma in an early stage. Eradication of H. pylori directly induces apoptosis in inflammation-related immunocytes in the gastric mucosa and this may be the mechanism for cure of low-grade gastric MALT lymphoma.

Though primary gastrointestinal MALT lymphoma can involve any part of the gastrointestinal tract from the esophagus to the rectum, primary duodenal MALT lymphoma is very rare. And little is known about the pathogenesis, presenting manifestations or treatment of duodenal MALT lymphoma, due to its rarity. The role of H. pylori in duodenal MALT lymphoma is also unclear. The cure of H. pylori infection has been correlated with tumor regression. Even in individual cases of lymphomas of small intestine, rectum and salivary glands, eradication of H. pylori can lead to complete remission of the tumor [11]. Nagashima et al. [12] reported regression of duodenal MALT lymphoma following eradication of H. pylori.

Treatment of primary gastrointestinal lymphoma varies from eradication of H. pylori to oncologic therapy including surgery, radiation, and chemotherapy with no consensus established on the most effective therapy. For low-grade gastric MALT lymphoma, the ideal treatment option should be the eradication of H. pylori associated with indolent nature and complete remission in approximately 80% of all patients [3]. Remission seems to be maintained in most cases for years. It is reported that gastric MALT lymphoma is currently the only cancer which can be treated by a simple antibiotic treatment. In clinical practice, a conservative approach with antibiotic eradication seems to be the primary choice for low-grade gastric MALT lymphoma, with oncologic therapy being reserved for those patients who fail to respond to H. pylori therapy.

Oncologic therapy can be used as single modality therapy and mostly in various combinations, which depends on the stage and biological rate of progression and transformation. As the incidence of late morbidity such as malnutrition and dumping is more common in patients treated with surgical resection, surgery in the treatment of primary gastric lymphoma is disputed [13]. Surgical resection may offer no survival benefit and in fact may be unnecessary in some patients.

As is known, MALT lymphoma is a highly chemo-sensitive disease. Many recent studies show that chemotherapy alone may be as effective particularly in primary gastrointestinal MALT lymphomas [14]. A controlled clinical trial showed that event-free survival was 52% in patients treated with surgery, 52% in the radiotherapy arm, and 87% in the chemotherapy group (p < 0.01), while the overall survival showed no statistical differences. It is considered that chemotherapy alone is an effective and safe therapeutic approach to primary gastric MALT lymphoma in early stages [15]. Moreover, as lymphoma is a systemic disease, a systemic approach like chemotherapy would be more appropriate. At the same time, chemotherapy has the advantage of organ preservation. In addition, it is effective for micro-metastases [1].

To our patient, eradication of H. pylori was given as the first step of treatment, followed by six cycles of CHOP. She responded rapidly to the treatment and no evidence of tumor deterioration was detected after 6 months. And a repeat MRCP came out to be normal which confirmed that the outlet of common bile duct was also involved.

**Conclusion**

Even though primary gastrointestinal MALT lymphomas are the most frequent sort of extranodal malignant MALT lymphomas, these tumors remain rare, which, together with the diversity of anatomical, clinical forms and endoscopic appearance, makes it difficult to conduct early diagnosis. As we know, low-grade gastrointestinal MALT lymphoma is a neoplasia with a favorable clinical behavior and an excellent prognosis, but has a possible transition to a high-grade MALT lymphoma. Rodriguez-Sanjuan et al. [16] reported that the 5- and 10-year survival rates were 90 and 75%. Therefore, early diagnosis of gastrointestinal MALT lymphoma becomes extremely important. Not only the diagnosis but also the treatment is not easy. Although many large series on treatment of primary gastrointestinal MALT lymphoma patterns have been published, the ideal treatment continues to be controversial. There is need to have prospective studies in the world by various centers to make treatment recommendations for patients with primary gastrointestinal MALT lymphoma.
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References


