Combined Adenocarcinoma and Mucosa-associated Lymphoid Tissue Lymphoma in Atrophic Gastritis: A Case Report and Review of the Literature

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Abstract

Atrophic gastritis is the process of chronic inflammation of the stomach mucosa that leads to the loss of gastric glandular cells. As a result, the stomach’s secretion of intrinsic factor is impaired, leading to vitamin B12 deficiency and megaloblastic anemia. Atrophic gastritis can be caused by persistent infection with Helicobacter pylori, which is believed to be a risk factor for gastric malignancy. A previously healthy 58-year-old woman gradually developed general malaise with dizziness and a feeling of abdominal fullness. A hemogram confirmed severe anemia (hemoglobin, 4.7g/dL; mean corpuscular volume, 123.7fL), leukopenia (white blood cells, 1,900/uL), and thrombocytopenia (platelets, 32,000/uL). Her vitamin B12 level was low. Upper gastrointestinal endoscopy revealed a pale and thin mucosa in the antrum and corpus with loss of gastric rugae over the cardia, compatible with an atrophic gastritis diagnosis. We performed randomized biopsies over the stomach. The patient underwent surgical intervention for an adenocarcinoma that was identified on the gastric biopsy, and pathological examination revealed combined adenocarcinoma and mucosa-associated lymphoid tissue lymphoma. After vitamin B12 replacement, the pancytopenia improved. We believe that physicians should be aware of this clinical presentation of atrophic gastritis and not neglect its potential malignant transformation in daily practice. (J Intern Med Taiwan 2013; 24: 227-233)

Key Words: Megaloblastic anemia, Atrophic gastritis, Vitamin B12 deficiency, Helicobacter pylori, Gastric adenocarcinoma, MALToma

Introduction

Atrophic gastritis is the process of chronic inflammation of the stomach mucosa1 in which the stomach’s secretion of intrinsic factor is impaired, leading to vitamin B12 deficiency and megaloblastic anemia. The following 2 types of atrophic gastritis are recognized: multifocal atrophic gastritis, which is the most common type and is caused by Helicobacter pylori infection2,3, and autoimmune atrophic gastritis1.

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carcinomas and gastric mucosa-associated lymphoid tissue lymphomas (MALTomas) are associated with
*H. pylori* infection. H. *pylori*-associated atrophic gastritis may develop lymphoid aggregates with
germinal centers that are essential for the development of MALTomas. As chronic inflammation
progresses, atrophy of the gastric mucosa is replaced by intestinal metaplasia and dysplasia or even intes-
tinal adenocarcinoma. Therefore, infection with *H. pylori*, a pathogen related to atrophic gastritis,
may play a significant role in the pathogenesis of the
simultaneous development of these tumors.

**Case Report**

A previously healthy 58-year-old woman gradually developed general malaise with dizziness
and abdominal fullness. She continued to feel fatigued with a poor appetite and gradually lost 8
kg over 4 months. During this period, she also noted progressive bilateral numbness of both hands. A
nerve conduction velocity examination documented mild sensory neuropathy and axonal degeneration.

![Image of endoscopy](image)

Figure 1. An upper gastrointestinal endoscopy revealed diffused mild oozing on the entire stomach and no defined
bleeder could be identified. Pale and thin mucosal change was noted in the antrum (a) and corpus (b)
compared with the normal antrum (A) and corpus (B); compatible with atrophic gastritis.
Adenocarcinoma and Mucosa-associated Lymphoid Tissue Lymphoma in Atrophic Gastritis

She thought the symptoms had been present for over 1 month but was not sure about the onset. She had visited a local medical doctor who immediately noticed pallor; however, the patient was unsure of it. A hemogram confirmed anemia, and she was told to visit a large hospital. The patient’s past medical history was unremarkable except for a remote appendectomy and an ectopic pregnancy many years earlier. She did not take any regular medications, and her diet included meat. The family history was non-contributory.

Because of the worsening malaise, she came to our emergency room, where an initial work-up revealed severe anemia (hemoglobin, 4.7g/dL; mean corpuscular volume, 123.7fL), leukopenia (white blood cells, 1,900/μL), and thrombocytopenia (platelets, 32,000/μL). An upper gastrointestinal endoscopy revealed diffused mild oozing throughout the stomach, but no defined bleeder was identified. Pale and thin mucosa was noted in the antrum and corpus with loss of gastric rugae over the cardia, compatible with an atrophic gastritis diagnosis (Figure 1). We performed randomized biopsies over the stomach. Testing for *H. pylori* was not performed. Tumor markers were unremarkable, as was a serum folic acid level, but her vitamin B12 level was low (71.80 pg/mL). A bone marrow aspiration showed hypercellular marrow with megaloblastic erythropoiesis and giant bands (Figure 2). Moreover, hypersegmented neutrophils in the peripheral blood were noted, a finding compatible with megaloblastic anemia (Figure 3).

The patient underwent surgical intervention because of an adenocarcinoma that was identified on the gastric biopsy. A total gastrectomy was performed due to the diffusely extended nature of the tumor. No obvious tumor or ulcerative lesion was seen in the resected stomach except for the loss of gastric rugae over the cardia. Histopathological evaluation of the resected stomach showed a background of atrophic gastritis with intestinal metaplasia and glandular dysplasia (Figure 4). A diffused-type, poorly differentiated adenocarcinoma with MALtoma coexisted and infiltrated the mucosa to the subserosa (Figure 5), while metastatic adenocarcinoma was noted in the lymph nodes. The pathology report revealed no *H. pylori* in the resected stomach, but serum *H. pylori* immunoglobulin G (IgG) tested positive. The patient had an uneventful recovery from the total gastrectomy. She has since received adjuvant

![Figure 2.](image-url) Bone marrow aspiration showed hypercellular marrow with megaloblastic erythropoiesis and giant bands. A megaloblast with increased nuclear/cytoplasmic ratio (arrow).

![Figure 3.](image-url) Hypersegmented neutrophil in the peripheral blood of the patient was noted compatible with megaloblastic anemia. A megaloblast with increased nuclear/cytoplasmic ratio (arrow).
chronic inflammation of the gastric mucosa with the loss of gastric glandular cells and replacement with intestinal-type epithelium, pyloric-type glands, and fibrous tissue. The following 2 types of atrophic gastritis are recognized: multifocal chronic atrophic gastritis and autoimmune chronic atrophic gastritis. In multifocal chronic atrophic gastritis, inflammation and atrophy are present in both the antrum and the corpus. *H. pylori* infection is considered the main etiologic factor of this form, making its eradication necessary. Conversely, in the autoimmune form of chronic gastritis, inflammation and atrophy are virtually restricted to the gastric corpus, and circulating parietal cell autoantibodies (PCAs) are detectable in the majority of affected patients. In our patient, an upper gastrointestinal (GI) endoscopy revealed a pale and thin mucosa throughout the stomach, whereas PCAs were undetectable. Serum *H. pylori* IgG tested positive. As such, we believed that *H. pylori* infection rather than an autoimmune condition was the etiologic factor of atrophic gastritis in our patient.

A megaloblast, the morphologic hallmark of megaloblastic anemia, is a product of impaired DNA formation, which in turn is due to deficiencies of vitamin B12 or folate. Vitamin B12 deficiency due to food–vitamin B12 malabsorption has been found to be associated with *H. pylori* gastritis in a wide range of age groups. Atrophic gastritis secondary to *H. pylori* infection is one explanation for vitamin B12 malabsorption. In this situation, low acid–pepsin secretion results in decreased release of free vitamin B12 from food proteins, which promotes overgrowth of the bacteria that bind vitamin B12 for their own use in the hypochlorhydric stomach and small intestine. Another suspected cause of vitamin B12 malabsorption in the setting of *H. pylori* gastritis is decreased secretion of intrinsic factor by parietal cells; however, a study demonstrated that this occurs infrequently.

Vitamin B12 deficiency affects the chemotherapy consisting of a combined cisplatin and 5-fluorouracil regimen. She was also treated with a parenteral vitamin B12 500 μg intramuscular injection daily for 1 week. The nerve conduction velocity examination was repeated 6 months later to document the reversibility of the neuropathy after the vitamin B12 treatment.

Discussion

Atrophic gastritis is characterized by the

Figure 4. (H&E stain, 40X). Histopathologic evaluation of the resected stomach showed background of atrophic gastritis with intestinal metaplasia (arrow head) and glandular dysplasia (arrow).

Figure 5. (H&E stain, 40X). Diffused type poorly differentiated adenocarcinoma (arrow head) with MALToma (arrow) coexist and infiltrate from mucosa to subserosa.
hematological, GI, and neurological systems. The most significant hematologic manifestation is megaloblastic anemia. A lack of vitamin B12 is associated with megaloblastosis of the GI tract epithelium, which results in anorexia and moderate weight loss. Neurological manifestations result from demyelination and are followed by axonal degeneration and neuronal death. Signs and symptoms include numbness and paresthesia in the extremities, weakness, and ataxia. Our patient presented with some of the above-mentioned signs and symptoms during the clinical course, but they resolved after vitamin B12 treatment.

Recent evidence suggested that both gastric carcinomas and gastric MALTomas are associated with *H. pylori* infection. Wotherspoon et al. reported a series of 9 cases of simultaneous adenocarcinoma and MALToma, however, *H. pylori* was described in only 7 of the 9 cases. Nakamura et al. reported a series of 12 patients with coexisting adenocarcinoma and MALToma, all of whom were infected with *H. pylori*. Our case showed synchronous gastric malignancies. The simultaneous development of synchronous gastric carcinomas is not unusual, as it is reported to occur in 1.25% of all gastric carcinomas. However, the coexistence of gastric adenocarcinoma and MALToma is a very infrequent event. Capelle et al. reported that 34 of 1,419 (2.4%) patients with gastric MALToma were diagnosed with gastric carcinoma. Morger et al. reported that 3 cases of early gastric carcinoma were identified in 120 patients with *H. pylori*-associated gastric MALToma. Montalban et al. reported that other cancers, primarily malignant lymphoma and gastric carcinoma, were detected in 16 of the 136 patients with gastric MALToma. Therefore, the simultaneous occurrence of gastric MALToma and gastric adenocarcinoma, such as in our case, appears very rare. Many more studies on the correlation between gastric MALToma and gastric adenocarcinoma are required.

The lack of pathological tissue proof of *H. pylori* is the limitation of our case report. The pathology report revealed no *H. pylori* in the resected stomach because as chronic inflammation progresses, the atrophic gastric mucosa is replaced by intestinal metaplasia. In the late stages of extensive atrophic gastritis, the number of *H. pylori* bacteria markedly decreases because the intestinal metaplasia creates an unfavorable environment for the pathogen. In such cases, the presence of *H. pylori* IgG may provide evidence of a past *H. pylori* infection.

In summary, atrophic gastritis is a process of chronic inflammation of the stomach mucosa. As a result of this, the stomach’s secretion of intrinsic factor is impaired, leading to vitamin B12 deficiency and megaloblastic anemia. Here, we reported a case of profound atrophic gastritis related to megaloblastic anemia. We believe that physicians should be aware of this clinical presentation of atrophic gastritis and not neglect its potential malignant transformation in daily practice.

References

萎縮性胃炎同時併存胃腺癌及粘膜相關淋巴組織淋巴瘤：病例報告及文獻回顧

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摘 要

萎縮性胃炎是指胃黏膜慢性發炎導致胃內的腺細胞減少，結果會影響到內在因子的分
泌，造成維生素B12不足及巨幼細胞性貧血。萎縮性胃炎造成的原因包括幽門螺旋桿菌感
染，而幽門螺旋桿菌本身也是被認爲會導致胃的惡性腫瘤。一位過去身體健康的58歲女性最
近感覺到全身疲累，頭暈及腹脹。血液檢查發現嚴重的貧血(血紅素：4.7g/dL，平均血球容
積：123.7fL)，白血球過低(白血球：1,900/uL)及血小板過低(血小板：32,000/uL)。另外她的
維生素B12指數也是低下。上消化道胃鏡檢查診斷萎縮性胃炎。後來她接受全胃切除手術，
原因是胃鏡的切片檢查結果是胃腺癌。全胃切除的病理報告是胃腺癌及粘膜相關淋巴組織
淋巴瘤。病人後來接受維生素B12的補給，她全血球減少症也獲得改善。對於巨幼細胞性貧
血，萎縮性胃炎必須列入繼發診斷，另外它轉移成惡性腫瘤的潛在性也必須要注