REVIEW ARTICLE

Autoimmune Metaplastic Atrophic Gastritis

Chitchai Rattananukrom MD[1], Narasak Changraksa MD[2]

[1] Division of Gastroenterology and Hepatology, Department of Internal Medicine, Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand

[2] Department of Internal Medicine,The 50th Anniversary Mahavajiralongkorn Hospital, Ubon Ratchathani, Thailand

Autoimmune metaplastic atrophic gastritis (AMAG) is a chronic progressive inflammatory condition caused by autoimmune destruction of the oxyntic mucosa in the corpus and fundus of stomach, sparing of antrum. The gastric mucosa is replaced by atrophic and metaplastic mucosa leading to progressive mucosal atrophy. Resulting in reduce or absent of acid production and loss of intrinsic factor may progress to a severe form of vitamin B12 deficiency anemia and iron deficiency anemia. Moreover, patients with AMAG have higher risks for gastric dysplasia, gastric adenoma, gastric adenocarcinoma, and gastric neuroendocrine tumor. The etiology of the development of AMAG is unclear.

The clinical presentations are usually non-specific signs or symptoms unless the degree of atrophy impairs the absorption of vitamin B12 and other substances, including folate and iron. Patients might have vague symptoms for many years before all reserves are depleted. Common clinical presentations are iron deficiency anemia and pernicious anemia.

The diagnosis of AMAG might be challenging and usually requires the combination of clinical and diagnostic tests such as laboratory tests, endoscopy, and histopathology. The management strategies are focused on the prevention of vitamin B12, folate and iron deficiencies. Rapid replenishment of vitamin B12 followed by lifelong maintenance on vitamin B12 is necessary when pernicious anemia is present. Patients should receive endoscopic follow-up every 3 to 5 years for surveillance of gastric cancer and neuroendocrine tumor.

Keywords: Autoimmune metaplastic atrophic gastritis; Diffuse corporal atrophic gastritis

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Autoimmune metaplastic atrophic gastritis (AMAG), also called diffuse corporal atrophic gastritis, is an autoimmune destruction of the oxyntic mucosa and is replaced by atrophic and metaplastic mucosa leading to progressive mucosal atrophy. Moreover, the inflammation is restricted to the corpus and fundus of stomach, sparing the antrum (corpus predominant) which distinguishes AMAG from other conditions leading to atrophic gastritis. The pathogenesis of AMAG causes reducing or absence of acid and pepsin production and loss of intrinsic factor leads to slowly decreasing patient's ability to absorb adequate quantities of iron and vitamin B12[1]. Therefore, there may progress to a severe form of vitamin B12-deficiency anemia known as pernicious anemia (PA) and also causes neurological complications, including paresthesia, loss of balance, and decreased memory. In addition, loss of parietal cells in oxyntic mucosa leads to high levels of gastrin production that can stimulate endocrine cells and develop gastric neuroendocrine tumors. Finally, the metaplastic changes in the mucosa are a known risk factor for gastric dysplasia, adenomas, and adenocarcinoma. The endoscopic and histologic findings of complete atrophy in the corpus and fundus of the stomach are well recognized in standard clinical practice. Thus, the diagnosis of AMAG can affect clinical management by preventing pernicious anemia and neurologic consequences of severe and chronic vitamin B12 deficiency[1].

Correspondence to:

Rattananukrom C.

Division of Gastroenterology and Hepatology, Department of Internal Medicine, Srinagarind Hospital, Khon Kaen University, Khon Kaen 40002, Thailand.

Phone: +66-43-363746

Email: Chitra@kku.ac.th

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Epidemiology

Due to the asymptomatic or pauci-symptomatic disease course and the lack of proactive screening strategies, the prevalence of AMAG is likely to underestimate, as it varies based on factors such as the clinical setting of enrollment, ethnicity, and diagnostic criteria applied. The prevalence of AMAG is estimated to be between 0.5 to 4.5% globally[2] depending on the setting of enrollment, age, sex, and ethnicity. AMAG is more commonly seen in females with female to male ratio of 3: 1, and the prevalence increases with age, being more common in those over 60 years of age[3]. The annual incidence of AMAG is 25 new case/100,000 people[2].

In terms of ethnicity, studies have shown that AMAG is more common in Caucasian populations than in other

ethnicities. In a retrospective Chinese study, the estimated annual detection rate of histologically and serologically diagnosed AMAG is found to be 0.9%[4]. Similarly, in a Japanese study, endoscopically and serologically confirmed AMAG is 0.49% of patients undergoing routine medical checks[5]. In one study, the prevalence of AMAG is higher in Italy than Asian jurisdictions, with 4.3% of patients being diagnosed with the condition[6]. Additionally, the central European histo-GERD trial estimates the prevalence of AMAG to be 2.3% in individuals undergoing gastric biopsy[7].

However, studies that estimated the prevalence of AMAG based on the presence of parietal cell antibodies (PCAs) or intrinsic factor antibodies (IFAs) have reported a higher prevalence (8 to 20%) than studies based on histology[8]. The prevalence of AMAG based on cases of pernicious anemia is estimated to be approximately 0.1% in the general population and 2% in individuals over 60 years of age[9].

AMAG is strongly associated with other autoimmune disorders, especially in type 1 diabetes mellitus and autoimmune thyroid disease[10]. The prevalence of AMAG in individuals with these conditions is reported to be 3 to 5 fold higher than general population[11]. Furthermore, AMAG and pernicious anemia might be underdiagnosed due to their asymptomatic nature and the variability in diagnostic criteria across clinical settings. Additionally, micro and macrocytic anemia is frequently treated with iron, folic acid, and cobalamin without further investigation into its underlying cause, potentially contributing to underdiagnosis. Biopsy samples of the gastric mucosa may also be inadequate or taken from the wrong location, further complicating diagnosis[12].

Pathogenesis

The etiology and exact causal agent are unclear due to several confounders and contributing factors that may interfere, such as low prevalence of AMAG, concurrent Helicobacter pylori-induced gastritis in many cases, and no or minimal manifestations in early stages of the disease[13].

The initial changes include infiltration of oxyntic mucosa by lymphocytes and plasma cells, consistent with the activation of an inflammatory process. The major drivers of the underlying autoimmune mechanisms of the disease are gastric H^+/K^+-ATPase reactive CD4 T-cells. This mechanism included destruction of the oxyntic mucosa from T-lymphocytes and production of anti-parietal cell antibodies (PCA) and anti-intrinsic factor antibodies (IFA) from B lymphocytes[8].

Several reports suggest that parietal cell death depends on Th1 CD4 T-cells and Fas/Fas-ligand, either through the interaction between infiltrating CD4 T-cells with gastric parietal cells that have up-regulated Fas expression or through homotypic interactions between parietal cells[14]. Hypochlorhydria develops as a result of the loss of oxyntic mucosa and disruption of maturation of parietal cells[15]. Serum pepsinogen I levels which produced in the oxyntic mucosa also decrease, as does gastric pepsinogen secretion. Furthermore, Absence of negative feedback from parietal cells induces G-cell hyperplasia and increased gastric secretion in the antrum, which leads to parietal cell pseudohypertrophy. This phenomenon cannot develop in atrophic glands, as anti-parietal cell antibodies also bind selectively to H^+/K^+ ATPase. Elevation of gastric secretion has direct effect in stimulation and proliferation of enterochromaffin-like (ECL) cells, which depends on severity. ECL hyperplasia may develop to dysplasia, neoplasia and can result in carcinoid tumor formation. The late phase, or the atrophic stage, is characterized by long standing inflammation that causes alteration of the major structural of glandular compartment, resulting in progressive loss of the native oxyntic glands. The most simple atrophic change involves the replacement of single glandular units by micro-scars of inflamed fibrous tissue due to the infiltration of immune cells. Atrophic change mostly coexists with metaplastic transformations, the development of metaplasia of the oxyntic glands. Two types of mucosal metaplasia usually coexist, pseudo-pyloric metaplasia and intestinal metaplasia (IM).

Pseudo-pyloric metaplasia ("oxyntic antralization") refers to the presence of mucus-secreting cells phenotypically resembling antral mucous cells develop in the oxyntic glands in corpus or fundus of the stomach. Most recently, a new term to describe pseudo-pyloric metaplasia, spasmolytic polypeptide-expressing metaplasia (SPEM), has been widely used. This term better reflects its molecular profile, rather than its histopathological appearance. SPEM is a preneoplastic gastric lesion that can also transform into intestinal metaplasia[16]. There are several theories have been proposed the etiology of SPEM as follows: 1) long standing inflammation of oxyntic mucosa, 2) acute direct effect of toxic substances on parietal cells (DMP-777)[17], and 3) trans-differentiation of chief cells[18]. Chief cells and SPEM express MAL2. This protein is considered the first trafficking protein and involved in vesicle trafficking, which is upregulated in SPEM[18].

Intestinal metaplasia (IM) is the replacement of glandular, foveolar and surface epithelium of gastric mucosa by intestinal epithelium. Two subtypes, small intestinal and colonic, have been described depend on the histological features. They can be classified into three types. Type 1, "complete", or small intestinal with brush border, characterized by the presence of goblet cells secreting sialomucins, columnar and/or Paneth cells. Type

2, "incomplete", or colonic type without brush border, contains goblet cells, but lack of columnar and/or Paneth cells. Type 3 is also "incomplete", or colonic type without brush border, and demonstrate the presence of goblet cells and the absence of columnar cells and/or Paneth cells, but predominantly expresses sulfomucins rather than sialomucins[19,20]. Inflammatory and hyperplastic polyps may develop in the later stages, and oxyntic mucosa can be totally absent in advanced disease of AMAG. In patients with AMAG with previous or concomitant *H. pylori* infection, atrophic metaplastic lesions might involve both antral glands (*H. pylori*-mediated) and corpus or fundus oxyntic mucosa (immune-mediated). The risk of gastric adenocarcinoma development is higher in such an extensive atrophic setting than in single or pure oxyntic gland-restricted autoimmune damage[21].

Genetic and environmental factors thought to play a role in the pathogenesis of AMAG. Autoimmune gastritis susceptibility genes, Gasa 1, 2, 3, and 4, have been discovered on chromosomes 4 and 6 and the H2 gene complex in murine models. Some of these genes are located on the same locus as mouse DM susceptibility genes, which may account for the strong association between AMAG and type 1 DM in humans[22].

Association with *H. pylori*

Many patients with AMAG have circulating antibodies to *H. pylori* and/or have *H. pylori* detectable in their gastric-oxyntic mucosa. Hence, *H. pylori* may play a role in the pathogenesis of AMAG[23,24]. On the contrary, patients with AMAG are less likely to be infected by *H. pylori*. The possible explanations are the metaplastic intestinal epithelium anh hypochlorhydria becomes unsuitable for *H. pylori* colonization[25].

For supportive evidence of association with *H. pylori*, The pathogenic mechanism of this process may cause by antigenic mimicry between *H. pylori* antigens and gastric H^+/K^+-ATPase or cross-reactivity. Many patients with *H. pylori* infection develop a wide spectrum of antibodies, which includes anti-foveolar, anti-canalicular and the classic PCA. These autoantibodies are directed against H^+/K^+-ATPase and disappear after eradication of infection.

Despite many overlaps in the course of the disease, it is important to differentiate AMAG from *H. pylori*-induced gastritis. AMAG affects only the body and fundus of the stomach, but H. pylori-induced lesions in multifocal pattern[26]. ECL hyperplasia and oxyntic gland involvement are more common in AMAG[13]. Parietal cell pseudohypertrophy is common in AMAG. However, it can be seen in *H. pylori* infection secondary to proton pump inhibitor use (Table 1).

Association with other autoimmune conditions

PCA are frequently present in patients with AMAG and can also be detected in patients with various other autoimmune diseases, explaining the association of these conditions with pernicious anemia. Patients with AMAG have a 3 to 5 times higher risk than the general population of developing further autoimmune diseases, such as chronic autoimmune thyroiditis, type-1 diabetes mellitus[3], vitiligo[27], Addison's disease[28], myasthenia gravis[29], oral erosive lichen planus.

AMAG has been reported in 24% to 35% of patients with autoimmune thyroiditis[30,31], especially Hashimoto's

Table 1. Comparison of autoimmune metaplastic atrophic gastritis (AMAG) with *H. pylori*-induced atrophic gastritis

Characteristics	Type of atrophic gastritis	
	Autoimmune metaplastic atrophic gastritis	*H. pylori*-induced gastritis
Pattern of distribution	Corpus and fundus (spare antrum)	Multifocal including antrum
ECL cell hyperplasia	Common	Rare
Parietal cell pseudohypertrophy	Common	Usually secondary to PPI use
Oxyntic gland involvement	Common	Rare
Inflammatory changes	Lymphocytes, plasma cells	Active inflammation, band-like lesions
Depth of inflammation	Lamina propria is usually involved	Superficial layers
Gastrin-17 level	High	Low but may be elevated
Pepsinogen I level	Low	Normal
Pepsinogen II level	Normal	Varies
Antibodies	Against parietal cells and intrinsic factor	Against H.pylori
Clinical manifestations	Asymptomatic or dyspepsia; symptoms of associated autoimmune conditions	Asymptomatic or dyspepsia
Risk of gastric neoplasms	Increased risk of gastric cancer and carcinoid	Increased risk of gastric cancer and carcinoid

H. pylori=Helicobacter pylori; ECL=Enterochromaffin-like; PPI=Proton pump inhibitor.

(Modified from Minalyan A, Benhammou JN, Artashesyan A, Lewis MS, Pisegna JR. Autoimmune atrophic gastritis: Current perspectives. Clinical and Experimental Gastroenterology. 2017;10:19-27)

thyroiditis, which is the most common association. The prevalence was higher (up to 45%) in older patients[32,33]. In type-1 diabetes mellitus, it has been observed that 6% to 10% of patients have concurrent AMAG[33,34], the prevalence increases with an age-dependent[35]. AMAG occurs in 10% to 15% of patients with polyglandular autoimmune (PGA) type-1 syndrome (hypoparathyroidism, Addison's disease, diabetes mellitus, and muco-cutaneous candidiasis) and in 15% of type-3 PGA patients (with diabetes mellitus and autoimmune thyroid diseases)[36].

Clinical manifestations

The clinical presentation is usually non-specific signs or symptoms unless the degree of atrophy impairs the absorption of vitamin B12 and other substances, including folate and iron. The development of vitamin deficiencies is a prolonged process. thus, patients might have vague symptoms for many years before all reserves are depleted which leads to substantial diagnostic delay. Common clinical presentation is indeed iron deficiency anemia, which might be present in up to 25 to 50% of patients with AMAG[37,38], whereas pernicious anemia might be found in up to 15 to 25% of patients[37,38].

Although some patients are asymptomatic until micronutrient deficiencies manifest, many patients complain of dyspepsia with postprandial distress. The most common initial findings were hematological disorders (37% of cases), followed by a histology positive for gastritis (34%), whereas in <10% of cases the clinical suspicion of AMAG was determined by the concomitant presence of other autoimmune diseases, neurological symptoms, or a positive family history[39].

Gastrointestinal manifestations

AMAG, resulting in hypo- or even achlorhydria, can impair gastric motility and might favor bacterial overgrowth in the small intestine, which are responsible for gastrointestinal symptoms. Most common symptoms are postprandial fullness, bloating, early satiety, nausea, and weight loss[40]. Atrophic glossitis has also been known as an early clinical manifestation of vitamin B12 deficiency, which usually presents as burning sensation of the tongue[41].

Hematologic manifestations

Anemia is the most characteristic feature that often leads to its diagnosis[42], fatigue and dyspnea may be present and might precipitate ischemic heart disease in more severely affected patients. One of the earliest presentations of AMAG is iron-deficiency anemia (IDA) which develops due to achlorhydria from oxyntic atrophy. Several studies have shown that refractory or unexplained IDA should increase suspicion of AMAG[37] and iron deficiency usually develops years before the depletion of cobalamin stores. Pernicious anemia characterized by vitamin B12 deficiency, macro-ovalocytes, anisocytosis, hyper-segmented neutrophils and, in some cases, pancytopenia. Vitamin B12 deficiency have been associated with increased risk of thrombosis likely as a result of hyperhomocysteinemia[13]. This, in turn, activates the coagulation system, increases platelet aggregation, and constricts vessels. Moreover, acute myocardial infarction and pulmonary embolism have been described in young patients with severe hyperhomocysteinemia secondary to pernicious anemia[43]. In late stages of AMAG, patients with combined vitamin B12 and iron deficiency are commonly observed and might have dimorphic anemia, which is usually characterized by normal mean corpuscular volume and anisocytosis[44].

Neurological manifestations

Neurological manifestations of vitamin B12 deficiency have been associated with demyelination due to impaired production of succinyl coenzyme A, which is essential for myelin sheath formation[45], followed by axonal damage and eventually neuronal death that might affect both the central nervous system and the peripheral nervous system[46]. Neurological symptoms may be present in the absence of hematological changes. The most prominent neurological manifestation is subacute combined degeneration (SCD) of posterior and lateral columns of the cervical and upper thoracic segments[47]. Patients may complain of a wide variety of symptoms including impaired sensory and peripheral nerve function, paresthesia, numbness, abnormal proprioception, ataxia, cognitive impairment, mood disorders, and overt psychosis. Neuropsychiatric conditions associated with pernicious anemia include depression, mania, obsessive-compulsive disorder (OCD), psychosis, and dementia[48]. This is the reason why it is crucial to early recognize and treat these patients with parenteral vitamin B12 in order to stop progression and improve neurological deficits which may not be reversible after therapy[49] (Table 2).

Diagnosis

The most common diagnostic tests for screening and confirming a diagnosis of AMAG are laboratory tests, endoscopy, and histopathology.

Laboratory testing

Effective method for screening and confirmation of AMAG is detection of target-specific antibodies. These following group is most widely used antibodies for the diagnosis of AMAG: PCA, IFA, and anti-*H. pylori* antibodies (anti-HP-IgM and anti-HP-IgG).

PCA is positive in the 85% to 90% of AMAG, with

Table 2. Main clinical manifestations of autoimmune metaplastic atrophic gastritis (AMAG)

Hematologic conditions	Gastroenterological conditions	Neurologic conditions
Macrocytic anemia	Dysmotility-type dyspepsia	Peripheral neuropathy
Non-anemic macrocytosis	Gastroesophageal reflux symptoms	Myelopathy
Iron-deficiency anemia	Delayed gastric emptying	Optic neuropathy
Coombs-negative hemolytic anemia		Autonomic dysfunction
Sideroblastic anemia		Depression
Pancytopenia		Mania
Pseudo-leukemia		Obsessive compulsive disorder
Pseudo-thrombotic microangiopathy		Psychosis
Thrombosis related to hyperhomocysteinemia		Cognitive impairment

(Modified from Massironi S, Zilli A, Elvevi A, Invernizzi P. The changing face of chronic autoimmune atrophic gastritis: an updated comprehensive perspective. Autoimmunity Reviews. 2019;18(3):215-22)

suboptimal specificity since they can be detected in other autoimmune disease, such as Hashimoto's thyroiditis and type-1 diabetes mellitus[8]. PCA identification can be made by immunofluorescence or ELISA techniques. However, ELISA was shown to be approximately 30 percent more sensitive than immunofluorescence[50]. Although an assay sensitivity of 82% and specificity of 90% was initially reported, current studies have shown excellent agreement between ELISA and immunofluorescence (75% for AMAG and 100% for pernicious anemia)[51]. PCA may rise, peak and fall over time in the natural history of AMAG, Thus, PCA may disappear in the late stages due to the progressive destruction of the gastric mucosa and consequent loss of target autoantigen. Identifying PCA and IFA in the same individuals significantly increased the diagnostic performance of ELISA, yielding a 73% sensitivity. IFA had an overall sensitivity of 60% and a specificity of 98% in diagnosing pernicious anemia and AMAG and its positivity has a good correlation with gastric atrophy[52].

Another diagnostic test that can be abnormal in patients with AMAG due to oxyntic gland atrophy is serum gastrin level (mainly Gastrin-17). Elevated gastrin production by G-cells in the antrum. The combination of measurements of PCA, IFA, serum gastrin, and anti HP-antibodies are also known as "serological gastric biopsy". It has been recognized to be effective for diagnostic purposes and highly correlates with the histological findings[53].

Serum biomarkers for gastric atrophy have been described in many studies, such as pepsinogen I (PGI), pepsinogen II (PGII), PGI: PGII ratio, and serum gastrin levels, in order to diagnose gastric atrophy without endoscopic biopsy. Pepsinogen I is secreted by chief cells of the oxyntic mucosa of gastric corpus and fundus and decreases in patients with AMAG. Whereas pepsinogen II is produced by the pyloric glands and decreases in patients with antral atrophy. Excellent concordance was observed between these serum biomarkers and gastric atrophy on histological examination. The PGI:PGII ratio with best cut-off value is 8 that showed the high sensitivity (71%), high specificity 71% high accuracy 71%, and the high negative predictive value (86%) for diagnosing gastric atrophy[54]. Hence, the pepsinogen I to pepsinogen II ratio is the most suitable and potential single measurement for screening for atrophic gastritis.

Serum vitamin B12 measurement was required in patients with laboratory confirm of macrocytic anemia. In case of suspicion of pernicious anemia without serum vitamin B12 level deficiency, measurement of homocysteine and methylmalonic acid (MMA) should be followed. However, it has also been shown that the serum level of all three tests (vitamin B12, homocysteine and MMA) can fluctuate over time and even be normal in cobalamin-responsive disorders[55].

The measurement of the plasma chromogranin A (CgA) level has been suggested for the diagnosis of AMAG, ECL hyperplasia and gastric carcinoids. CgA levels have been found to correlate well with the degree of ECL hyperplasia in patients with AMAG. The levels of CgA can be affected by other conditions which can lead to false-positive results, including in inflammatory bowel diseases, hepatocellular carcinomas, non-alcoholic fatty liver disease, renal insufficiency or chronic use of proton pump inhibitors[56].

Endoscopy

Upper gastrointestinal endoscopy is usually performed to get gastric biopsies and obtain histopathological diagnosis, which are necessary to establish an accurate diagnosis. In the early disease stage, the gastric mucosa does not display any specific morphological alterations. The development of frank atrophy markedly alters the gross mucosal appearance, flattened rugal folds and submucosal vessels may be visible (Figure 1), and pseudopolyps or polyps (hyperplastic or adenomatous) might be present. Gastric tissue samples should be obtained for assessing the presence, grade, and etiology of the gastritis. According to the updated Sydney system recommendations, five biopsy

samples should be obtained, two from the corpus, two from the antrum and one from the incisura angularis[57].

Histopathology

Biopsy is considered the most reliable method for the diagnosis of metaplastic atrophic gastritis but when severe inflammation is present, it is hard to reliably evaluate the presence of atrophy.

Pathological samples obtained from the distal antral mucosa usually do not show inflammatory or atrophic changes. Pathological samples from transitional areas where mucosecreting and oxyntic glands coexist might display inflammatory lesions, including a dense monocytic infiltrate (Figure 2). A normal antrum but inflamed oxyntic mucosa should point to early-stage AMAG.

Several histopathological changes have been suggested that may be characteristic of AMAG. The early phase includes the infiltration of plasma cells and lymphocytes in lamina propria, with a mainly top-down gradient and the patchy destruction of oxyntic glands along with spasmolytic polypeptide-expressing metaplasia (SPEM) or intestinal metaplasia (IM)[13]. The pseudo-hypertrophy of the remaining parietal cells may also be present. In a later phase, dense plasma cells and lymphocytes infiltration and atrophic glandular alterations become clearly visible, with oxyntic antralization, the replacement of the native population of parietal cells by a new phenotype of clear, muco-secreting epithelia, with the phenotype of antral glands. These features are sufficiently to supports the diagnosis of AMAG, especially if there is no inflamed or atrophic antrum.

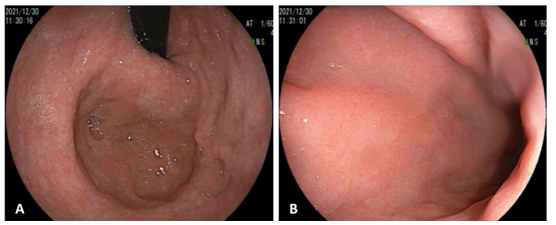

Figure 1. Endoscopic appearance of the stomach of a patient with overt AMAG shows gastric atrophy. Flattened rugal folds and visible sub-mucosal vessels is seen in gastric fundus (A) and gastric corpus (B). [Courtesy of C. Rattananukrom, Khon Kaen University, Thailand].

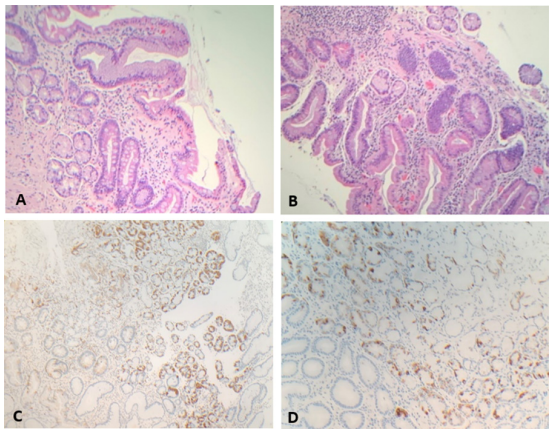

Figure 2. Histopathology of gastric fundus in AMAG show gastric gland atrophy, lymphocytes infiltration in lamina propria and intestinal metaplasia (A, B H&E staining). Immunohistochemistry for Synaptophysin (C) and Chromogranin A (D) reveal the hyperplastic ECL cells. [Courtesy of Department of Pathology, Khon Kaen University, Thailand].

Advanced AMAG is characterized by "oxyntic mucosa desertification" (i.e., oxyntic glandular units are replaced by fibrosis of the lamina propria), foveolar hyperplasia and the formation of hyperplastic and inflammatory polyps[2]. Pseudo-pyloric, pancreatic and intestinal metaplasia becomes widespread and inflammation is generally minimal. Late-stage lesions mostly coexist with prominent ECL cell hyperplasia, including linear and nodular hyperplasia, or ECL cell dysplasia which is the precursor of gastric carcinoid tumors. Immunohistochemistry may facilitate by identifying hyperplastic ECL cells via chromogranin (CgA) or synaptophysin immunoreactivity. Rarely, AMAG progresses to diffuse (complete) gastric atrophy[11].

The location of inflammation and atrophy, along with the presence or absence of *H. pylori*, are used for classifying gastritis and as an indicator of its etiology. The Operative Link on Gastritis Assessment (OLGA) is another scoring system proposed specifically in order to assess the severity by distinguishes severity for gastric atrophy into four stages. The OLGA score takes account into both antrum and corpus atrophy. The advantage of this scoring system is its ability to stratify patients according to the risk of developing gastric adenocarcinoma. Patients with OLGA Stages III and IV are associated with a higher risk of gastric cancer development. An alternative staging system, operative link on gastric intestinal metaplasia assessment (OLGIM), has been proposed. OLGIM considers only intestinal metaplasia for the staging of gastric atrophy, but it can underestimate the grading of atrophy as it excludes both non-metaplastic and pseudo-pyloric metaplasia from the atrophy score[11].

Neoplastic complications

The incidence of gastric neoplasms is higher in patients with AMAG compared to the general population[11]. Overall, AMAG has been associated with the development of two types of gastric neoplasms: intestinal type gastric adenocarcinoma and type I gastric neuroendocrine tumor.

Gastric adenocarcinoma (GA)

Intestinal metaplasia and concurrent *H. pylori* infection are two main factors that have been known the risk of Gastric adenocarcinoma in AMAG patients, but mainly *H. pylori*-

related. The incidence of developing gastric adenocarcinoma in AMAG range between 0% and 1.8% per year[57]. Extensive mucosal atrophy has been linked to an increased risk of gastric cancer. A pooled gastric cancer incidence rate of 0.27% per person-years and an estimated nearly seven-fold relative risk of gastric cancer for pernicious anemia patients. The neoplastic risk increases according to the extent and duration of atrophy[58].

Type-1 gastric neuroendocrine tumor (type-1 gNEN)

AMAG is associated with increased risk of the development of Type-1 gNENs. The incidence variable from 0.4% to 7% of the AMAG patients screened by endoscopy[59]. The pathologic changes are initiated by the loss of negative feedback by parietal cells on gastrin secretion. Hypo-/achlorhydria subsequently results in hypergastrinemia which causes ECL hyperplasia that could progress to dysplasia and neuroendocrine tumor. The most important risk factors are male gender, chromogranin A levels >61 U/L, and presence of intestinal metaplasia. There is evidence in other systems that pro-inflammatory cytokines, such as TNF-α, may contribute to neuroendocrine cell differentiation/hyperplasia[2].

Endoscopic surveillance

Patients with autoimmune gastritis may benefit from endoscopic follow-up with histological confirmation at 3 to 5 year intervals[60].

Treatment

The management strategies of the early stages of autoimmune atrophic gastritis is focused on the prevention of vitamin B12, folate and iron deficiencies. Adequate supplementation of these substances will effectively prevent vitamin B12 depletion and the development of anemia. Hematological alterations are usually reversible upon treatment, but neurological alterations might be irreversible. No anti-inflammatory, immunosuppressive or biological therapy is available for treatment despite AMAG being an immune-mediated condition, mostly owing to lack of studies testing different drugs[11].

When pernicious anemia, with or without extra-hematologic manifestations of vitamin B12 deficiency, is present, the initial strategy involves the rapid replenishment of vitamin B12 deficiency by parenteral supplementation followed by lifelong maintenance on vitamin B12, and oral iron supplementation are needed for full hemoglobin response. Initial therapy is 1,000 μg of vitamin B12 intramuscularly daily or every other day for a week, followed by a weekly administration for 1 to 2 months and then monthly lifelong[61]. High replacement doses, orally, of 500 to 1,000 μg a day seem to be effective in case of little atrophy[62]. For maintenance, oral supplement and parenteral administration with vitamin B12 can theoretically be equally effective because oral vitamin B12 absorption takes place by simple diffusion through the intestinal wall, but only when administer in high doses of the vitamin.

The vitamin B12 therapy reverses all abnormal hematologic changes. Serum MMA and plasma homocysteine levels normalize within the first 5 days to 2 weeks[46], and of serum vitamin B12 after 2 weeks of treatment. During the first month of treatment, macrocytosis generally disappears, whereas the normalization of hemoglobin would take longer. The neurological symptomatology response depends on the severity of symptoms and duration before the beginning of treatment[63].

Other micronutrient deficiencies, folate or 25-OH vitamin D, should be regularly checked, since they have been reported in AMAG patients. In case of deficiency of these micronutrients, specific supplementation is indicated.

Several studies have been confirmed that *H. pylori* infection can induce autoimmune process in the gastric lining including oxyntic mucosa, eradication of *H. pylori* can decrease the levels of antibodies associated with AMAG and has been proven effective to cure early stages of autoimmune gastritis[64].

Conclusion

AMAG is a chronic progressive inflammatory condition that results in the replacement of the normal oxyntic mucosa in the gastric corpus by atrophic and metaplastic mucosa, leading to a corpus predominant atrophic gastritis. Resulting in reduce or absent of acid production and loss of intrinsic factor may progress to a severe form of vitamin B12-deficiency anemia known as pernicious anemia and iron deficiency anemia. Moreover, patients with AMAG have higher risks for gastric adenocarcinoma and gastric neuroendocrine tumor. Laboratory abnormalities that are associated with AMAG include hypergastrinemia, IDA, PCA and IFA, and vitamin B12 deficiency. IFA are less sensitive for AMAG but more specific, whereas PCA are more sensitive but less specific. The diagnosis might be challenging and the clinical presentation may be more variable. AMAG should also be considered in presence of other autoimmune disease, especially chronic autoimmune thyroiditis and type 1 diabetes mellitus. The management strategies are focused on the prevention of vitamin B12, folate and iron deficiencies. When pernicious anemia is present, the management involve rapid replenishment of vitamin B12 deficiency followed by lifelong maintenance on vitamin B12. Patients with AMAG should receive endoscopic follow-up every 3 to 5 years for surveillance of gastric cancer and neuroendocrine tumor.

What is already known on this topic?

Because of the variety of clinical presentation in AMAG. Physicians should be concern and aware of this disease. Management should be better with multidisciplinary team involving gastroenterologists, pathologists, internists, and other specialists depending on the clinical manifestation.

What this study adds?

This review describes current knowledge of AMAG which is the complex and multifaceted condition. There are many unmet needs and uncertainties still exist even though recent advance understanding of this disease. Further study of the pathogenesis, diagnosis, treatment, and prevention is still necessary.

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Potential conflicts of interest

The authors declare no conflict of interest.

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