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ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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MINIREVIEWS

Update understanding on diagnosis and histopathological examination of atrophic gastritis: A review

Xiu-Zhen Ma, Ni Zhou, Xiu Luo, Si-Qi Guo, Ping Mai

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Abstract

Chronic atrophic gastritis (CAG) is a complex syndrome in which long-term chronic inflammatory stimulation causes gland atrophy in the gastric mucosa, reducing the stomach's ability to secrete gastric juice and pepsin, and interfering with its normal physiological function. Multiple pathogenic factors contribute to CAG incidence, the most common being *Helicobacter pylori* infection and the immune reactions resulting from gastric autoimmunity. Furthermore, CAG has a broad spectrum of clinical manifestations, including gastroenterology and extra-intestinal symptoms and signs, such as hematology, neurology, and oncology. Therefore, the initial CAG evaluation should involve the examination of clinical and serological indicators, as well as diagnosis confirmation *via* gastroscopy and histopathology if necessary. Depending on the severity and scope of atrophy affecting the gastric mucosa, a histologic staging system (Operative Link for Gastritis Assessment or Operative Link on Gastritis intestinal metaplasia) could also be employed. Moreover, chronic gastritis has a higher risk of progressing to gastric cancer (GC). In this regard, early diagnosis, treatment, and regular testing could reduce the risk of GC in CAG patients. However, the optimal interval for endoscopic monitoring in CAG patients remains uncertain, and it should ideally be tailored based on individual risk evaluations and shared decision-making processes. Although there have been many reports on CAG, the precise etiology and histopathological features of the disease, as well as the diagnosis of CAG patients, are yet to be fully elucidated. Consequently, this review offers a detailed account of CAG, including its key clinical aspects, aiming to enhance the overall

understanding of the disease.

Key Words: Atrophic gastritis; *Helicobacter pylori* infection; Autoimmune gastritis; Diagnosis; Operative link for gastritis assessment staging; Gastric cancer risk

Core Tip: Chronic atrophic gastritis (CAG) is a complex syndrome with multiple pathogenic factors, broad and non-specific clinical manifestations, and it is often seen as fragmented by each expert in their specific field of expertise, making diagnosis difficult and the exact histopathological features unclear. Therefore, this review used a thematic analysis approach, focusing on studies related to the diagnosis, histopathological examination, etiology, clinical manifestations, and management of CAG. Priority was given to recent studies (within the last 10 years) to ensure that the review reflects the most current understanding of CAG. To enhance the understanding and diagnostic ability of clinical doctors towards CAG.

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INTRODUCTION

Chronic atrophic gastritis (CAG), also known as atrophic gastritis (AG), is a chronic disease caused by multiple factors. This disease is mainly characterized by the ultimate loss of gastric mucosal glands. The quantity of parietal cells reduces when a lesion affects the gastric body, impairing the secretion of gastric acid and intrinsic factors, thereby compromising the absorption of essential micro-nutrients like iron and vitamin B_{12}. This chain of events could ultimately lead to anemia [1]. Gastric cancer (GC) often originates through a progression from chronic gastritis to AG, and then to intestinal metaplasia (IM), and ultimately to carcinoma, partly as a direct result of active inflammation. In this regard, AG is considered the initial phase in a multistage process preceding cancer development. As the disease worsens, it progresses to more severe stages, including IM and eventually gastric malignancy. Furthermore, AG patients could experience changes in their intragastric microenvironment, another phenomenon that could increase the risk of GC development[2]. Although the precise etiology of AG remains debatable, long-term *Helicobacter pylori* (*H. pylori*) infection, various autoimmune responses, and primary autoimmune diseases are generally believed to be its primary causes[3]. Most AG patients are asymptomatic in the early stages. They may also show non-specific symptoms in the late stages, including upper gastrointestinal (GI) symptoms, autoimmune diseases, and pernicious anemia. Continuous stimulation of gastrin-secreting cells in the gastric antrum (with intestinal chromaffin cell hyperplasia) could result in the incidence of type-I gastric neuroendocrine tumors in some patients[4,5]. Therefore, screening for AG should be performed in all these relevant high-risk groups. Although AG diagnosis is challenging, serologic testing for the detection of antibodies against *H. pylori* appears to be a non-intrusive, dependable approach. Chronic autoimmune AG (CAAG) diagnosis should also consider screening for autoantibodies and serum pepsinogen I and II (PGI and II) to identify patients that require gastroscopy[1]. Irrespective of the underlying etiology, histopathological confirmation is imperative for AG diagnosis.

Despite having significant clinical implications, AG often fails to attract commensurate research attention, partly due to experts regarding it as a phenomenon with fragmented clinical knowledge. As a result, the limited independent exploration of AG treatment over the years has somewhat impeded the worldwide obtainment and integration of knowledge and insights on this crucial precancerous lesion. This review searched PubMed for updated literature in recent years and retrieved previously published articles from the reference list. Herein, we explored the etiology, clinical symptoms, diagnosis, and histopathological features of AG in a large cohort of AG patients with distinct clinical manifestations, aiming to improve AG diagnosis and treatment and provide surveillance recommendations for enhancing the approaches for monitoring AG patients. This review synthesized findings from a broad range of peer-reviewed studies published in the last decade, concentrating on high-impact journals and seminal works in the field. The literature selection was guided by relevance to the diagnosis, histopathological examination, and etiology of AG. Studies that provided new insights or comprehensive reviews of existing knowledge were prioritized. To ensure a balanced and accurate overview, conflicting findings were included and critically assessed. While the study did not present new experimental data, it could play a notable role in summarizing and integrating existing research, which is vital for understanding the current state of the field and guiding future research directions.

TIOLOGY AND RISK FACTORS

It is well known that *H. pylori* infection and autoimmune diseases are the main AG culprits. On the one hand, *H. pylori*

infection causes gastritis by adhering to the gastric epithelium *via* certain proteins located in the outer membrane, such as Adhesion lipoproteins A and B, blood type antigen binding adhesive proteins, and sialic acid-binding adhesion proteins, and entering the stomach's intrinsic layers through the flagellar structure. Within the intragastric environment, *H. pylori* infection develops two key adaptations for its survival. First, it bypasses the bactericidal effect of gastric acid and the scavenging effect of autoimmunity. The other adaptation is urease production, promoting its perseverance within the acidic surroundings of the stomach and infectivity potential[6,7]. Furthermore, the primary mechanism of *H. pylori*-induced cellular harm is attributed to the actions of two distinct genetic elements: Vacuolar cytotoxin A and the cytotoxin-associated gene a protein (CagA). A study revealed that compared to uninfected individuals, invasive non-cardiac cancer incidence rates in individuals infected with *H. pylori* but not expressing CagA and infected individuals expressing CagA were 5.2 times and 18.2 times, respectively[8]. Thus, chronic *H. pylori*, as well as the virulence of bacterial populations and their induction of mucosal inflammation, gradually destroys gastric glands, ultimately causing multifocal AG. Prolonged utilization of proton pump inhibitors (PPIs) could induce or exacerbate AG development in individuals with *H. pylori* infection[9]. A comprehensive meta-analysis revealed that while first-degree relatives of GC patients were at a remarkably increased danger of AG, those with *H. pylori* infection had a significantly higher CAG risk [10].

Furthermore, a series of autoimmune reactions in the body directly target and damage the gastric gland's parietal cells, severely impairing gastric acid secretion and causing hypochlorhydria, which in turn induces hypergastrinemia and triggers CAAG with APCA positivity and vitamin B_{12} malabsorption[11]. There is substantial evidence linking cancer progression with hypoacidity (mainly associated with atrophy), supporting the hypothesis that diffuse and intestinal GCs originate from non-metaplastic atrophy. After gastric mucosal atrophy, the gastric microenvironment "reshapes" into a milieu conducive to GC development[12]. In this regard, whether IM should be considered a precancerous lesion arising from GC remains debatable. Although revisiting the long-standing presumption that IM serves as the initial stage of gastric carcinogenesis stage is imperative, we must also embrace a broader perspective that considers atrophy the fundamental "cancer field" for gastric adenocarcinoma[13]. According to Engstrand and Graham[14], a synergistic effect could arise from the interaction between the microenvironment with genotoxic-induced atrophy (which may involve changes in the microbiota) and the *H. pylori* infection-induced pro-cancer inflammatory cascade reaction[14]. A study comparing differences in the distribution of gastric flora between CAG cases and non-CAG controls found that the complexity, abundance, and diversity of bacteria in CAG patients decreased, whereas GC exhibited an even lower bacterial diversity or abundance. As reported for other GI and non-CAG diseases, loss of microbiota diversity implies the presence of an aberrant ecosystem. The contrasting intricacy and structure of bacterial populations in CAG subjects relative to healthy controls might stem from a gastric acid secretion-induced pH decrease in CAG patients, which, in turn, triggers changes in the intragastric environment[15]. Therefore, atrophy assessment requires a comprehensive score of all histological lesions contributing to "loss of native glandular units". However, the significance of atrophied gastric microbiota in cancer promotion requires further investigation.

Other factors contributing to AG development include excessive salt consumption, regular smoking, and obesity. According to research, excessive salt intake could increase the vulnerability to *H. pylori* infection and the risk of developing GC in AG patients. Consequently, adopting a low-salt diet might diminish the risk of GC development[16, 17]. It has also been reported that alterations in AG and IM may increase the risk of GC development among male smokers[18]. In the Korean populace, research evidence suggested that the risk of developing AG and IM increased with the baseline body mass index category[19]. Furthermore, AG is relatively common among older adults but with wide variations in its prevalence across regions, ethnicities, and gender, among other parameters. Interestingly, a Swedish study revealed that AG prevalence is increasing among younger individuals and is significantly higher in women than in men[20]. In compiling this review, studies were selected based on their methodological relevance to the etiological factors and risk contributors to AG. Emphasis was placed on research with robust sample sizes, clear diagnostic criteria, and studies that utilized advanced histopathological techniques. Analytical frameworks that explored the multifactorial nature of AG, particularly those incorporating both clinical and molecular data, were prioritized.

CLINICAL MANIFESTATIONS

Given that it could manifest *via* a variable spectrum of signs and symptoms, CAG should be considered a multifaceted disorder. This review focused on autoimmune CAG, particularly *H. pylori*-associated CAG (*H. pylori* CAG), which has limited clinical data. Due to the gradual onset of micronutrient inadequacies, CAG may be clinically insidious for numerous years in some instances; hence, patients are often diagnosed in the late stages[21]. Furthermore, from a gastroenterological perspective, it is conventional practice to consider the clinical manifestations of CAG as insidious. On the other hand, research indicated that individuals diagnosed with CAG often experience GI symptoms, most commonly early satiety and postprandial fullness[22]. Dysmotility dyspepsia alone has been reported in approximately 70% of the patients, and approximately 25% of autoimmune CAG patients experience various symptoms of gastroesophageal reflux, such as a burning sensation and acid reflux[23]. Despite the presence of the aforementioned GI symptoms, none of them was deemed clinically significant in relation to autoimmune CAG. We observed several features clearly associated with hematology, neuropsychiatry, and gastroenterology. The most common finding was hematologic abnormalities (47%), followed by a histological diagnosis of gastritis in 34% of the cases. On the other hand, in < 10% of the examined cases, clinical suspicion of CAAG was jointly confirmed by the presence of other autoimmune diseases, neurological manifestations, or a positive family history of GC[24]. Pernicious anemia is a common hematological manifestation of CAAG, appearing as a late CAAG complication in 54%-62% of patients. An observational study of autoimmune CAG

demonstrated that atrophy of the gastric mucosa and lamina propria glands, as well as a significant reduction in gastric acid secretion, occur when CAG affects the mucosa of fundic glands. This led to a shortage of micronutrients such as vitamin B_{12} and iron and hematologic manifestations, including macrocytic anemia, iron-deficiency anemia, and periplasmic cytopenia in 3.4% of the patients[5]. According to reports, insufficient iron anemia could occur before the onset of vitamin B_{12} deficiency and pernicious anemia, especially in young female patients, accounting for 35%-58% of cases[25]. In a previous study, iron deficiency anemia was found in 83 (52%) of the 160 CAAG patients involved, implying that this condition may be the most prevalent hematological symptom of CAAG[26]. Furthermore, vitamin B_{12} deficiency could lead to impaired neuronal myelin formation; specifically, myelination, which is facilitated by Schwann cell axons and myelin phospholipids, could cause neuronal damage and peripheral neuropathy[27,28]. Additionally, a study comparing the general condition and peripheral nerve conduction velocity of CAG patients discovered a significant downregulation of serum vitamin B_{12}, which is correlated with the occurrence of peripheral neuropathy[29]. Additionally, vitamin B_{12} and folate deficiency in CAG patients could cause hyperhomocysteinemia, increasing the risk of cardiovascular diseases and thrombosis. Nonetheless, no meaningful correlation was found between CAG patients and mortality or CVD in a sizable cohort study conducted in Germany[30]. Notably, vitamin B_{12} deficiency also causes cognitive, mood, and behavioral changes, necessitating prompt treatment to avoid irreversible neurological damage and reduce morbidity[31].

Among the CAAG-associated autoimmune diseases, AITD and type I diabetes are the most common. The risk of CAAG in patients with these two autoimmune diseases appears to be 3-5 times higher[32]. Furthermore, there are reports of CAAG prevalence in 24%-35% of patients with autoimmune thyroid diseases, especially Hashimoto's thyroiditis, which has an incidence rate as high as 45% in elderly patients[33]. There are some interesting similarities between the two diseases. The thyroid gland and the stomach share an embryonic origin, tracing back to the primitive gut. Additionally, gastric mucosal cells and thyroid follicular cells have displayed a parallel function in iodine concentration and transportation to their cellular membranes. This mechanism, which is crucial for thyroid hormone synthesis, also regulates gastric mucosal cell proliferation. Other relevant autoimmune diseases include Addison's disease, celiac disease, vitiligo, and rheumatoid arthritis[34], but the relationship between them is yet to be fully elucidated, and existing evidence is insufficient.

In some instances, CAAG could also lead to multiple tumors, among other complications, such as gastric mucosa atrophy, a condition that may progress to the formation of gastric neuroendocrine neoplasms (gNETs) and gastric adenocarcinoma. The formation of gNETs involves a multistep process originating from intestinal chromaffin cells. Since hypergastrinemia is crucial in sustaining intestinal chromaffin cell proliferation, it may promote gNET development[35]. Based on their site of origin and patients' clinical characteristics, gNETs could be classified into three groups: Types I, II, and III, with type I being the most common and accounting for 80% of cases[36]. Type I gNETs are associated with CAAG occurrence, for which the key risk factors include the male gender, chromogranin A level > 61 U/L, and IM presence[37]. A surveillance-based, epidemiologic case-control study revealed that PA patients were more likely to develop both type I and type II gNETs[38]. Since gNETs are largely asymptomatic, they are often detected incidentally during endoscopic examination. Notably, an early gNET diagnosis has a better prognosis than a late diagnosis[39]. Although the role of hypergastrinemia in CAAG progression to gNETs has been confirmed, the precise role of immune mechanisms remains unclear. However, evidence suggests that pro-inflammatory cytokines, such as TNF-α, may promote neuroendocrine cell differentiation/proliferation in other systems[40].

DIAGNOSTIC WORKUP

Histopathological examination is the gold standard for CAG diagnosis. However, there other non-invasive tests that could aid in diagnosing cases of clinically suspected CAG. In some studies, CAG detection relied on alternate serological indicators of gastric function, specifically the pepsinogen I to pepsinogen II ratio or just pepsinogen I. Serological testing of autoantibodies may or may not be considered a clinical auxiliary diagnosis avenue. In all cases, high-resolution color endoscopy should be employed, as it can increase the likelihood of detecting tiny lesions. Moreover, *H. pylori* infection is another CAG risk factor that must be excluded through histological examination, especially if histologically questionable findings (such as active gastric mucosa inflammation, atrophy of the sinus or gastric angle notch) were found *via* antigenic stool examination. Therefore, assessing changes in AG using non-invasive or invasive methods may reveal a patient's risk of GC development.

Non-invasive testing

Serologic diagnosis: Serologic testing is the ideal choice for CAG detection and screening of high-risk populations. Serum biomarker testing should screen for gastric H+/K+ ATPase-related autoantibodies and anti-*H. pylori* antibodies. Furthermore, alterations in atrophy correlate with gastric acid output and the production/secretion of gastrin-1 (G-1) and pepsinogen I and II (PgI and PgII). In this regard, proteasogen I and II, as well as G1 assays, could be employed as reliable non-invasive avenues for test screening using a combination of PgI, PgII, PgI/PgII ratio, and G-1 for accurate detection of CAG presence[41]. It could also be used to screen high-risk populations for CAG to determine patients whose diagnosis should be histologically confirmed through gastroscopy and gastric biopsy. A study revealed that the ratio of PGI to PGII exhibited the highest sensitivity (96.1%) and negative predictive value (NPV; 97.7%), whereas, individually, PGI demonstrated the highest specificity (94.6%), and PGII had a substantial NPV (90%). However, anti-*H. pylori* IgG antibodies displayed comparatively lower sensitivity and specificity at 58.8% and 26.5%, respectively. These findings suggest that the PgI/PgII ratio is the most suitable standalone marker for AG detection. Furthermore, lower PGI/PGII

ratios were correlated with CAG[42,43]. The diagnostic efficacy of G-1 has also been reported to be higher in CAAG patients [area under the curve (AUC) = 0.83] than in *H. pylori* AG patients (AUC = 0.62)[44]. Therefore, in CAAG, it appears reasonable to assess plasma G-1 annually, with endoscopy performed, if there is an increase, especially if it is significant (> 100 pg/mL)[45]. It is well known that CAAG is linked to gNET progression. According to research, patients with CAAG combined with gNETs often exhibit a low PGI/PGII ratio and high G-1 levels. Compared to those without gNETs, CAAG patients with gNETs had a PGI/PGII ratio < 2.3 and G-1 Levels > 29.6 pmol/L[46]. Therefore, the detection of PGI, PGII, and G-1 Levels in CAAG patients might help identify those at a high risk of gNETs.

To determine the autoimmune basis of gastric atrophy, physicians should also test for parietal cell antibodies and internal factor antibodies in patients whose histology is consistent with CAAG. Although APCA is widely regarded as the most sensitive serum biomarker for diagnosing autoimmune CAG, false positives are not rare, as APCA can also be upregulated in *H. pylori* infection and other autoimmune diseases[47]. A case-control study showed comparable APCA-positive rates between *H. pylori* CAG and CAAG patients[48], implying that APCA positivity is not a unique CAAG feature and that it can be detected in the damaged mucosa of all CAG patients. In this regard, APCA levels may be useful in diagnosing gastric mucosal injury in CAG patients. Moreover, in line with a prospective study which reported that APCA predicts the trend of disease evolution in CAG, with its levels gradually rising over time, peaking, and then decreasing, ultimately fluctuating and disappearing with the gradual destruction of the gastric mucosa, APCA levels may be undetectable in the late stages of CAAG[25]. On the other hand, IFAB demonstrated low sensitivity (< 30%) but high specificity in multiple studies and was found to be positive in the later stages of the disease[48]. Additionally, PA patients often exhibit positive IFAB, APCA, and/or megaloblastic bone marrow changes, as well as elevated levels of plasma homocysteine and methylmalonic acid. To determine the risk AG stratification in the gastric corpus and exclude common gastric tumors, such as NETs, patients clinically diagnosed with pernicious anemia who have not recently undergone endoscopy should be subjected to endoscopy along with a biopsy[49].

Other recommended serum biomarkers for gastric atrophy, such as the serum growth hormone-releasing peptide (ghrelin), a molecule predominantly secreted by the endocrine cells lining the gastric mucosa, has emerged as a highly promising gastric atrophy biomarker. According to recent reports, serum ghrelin detection exhibited remarkable sensitivity and specificity in identifying gastric atrophy, reaching 93% and 100%, respectively. This performance surpasses that of the PgI/II ratio and gastrin[50]. Although research has presented serum ghrelin as the most sensitive and specific non-invasive biomarker for CAG[51], further studies are required before its clinical application.

Invasive testing

Endoscopic evaluation for AG: The endoscopic diagnosis of CAG can be difficult as the visual appearance of some of the disease's features could be subtle. To maximize diagnostic accuracy, the endoscopist should first perform high-quality examinations per existing systematic methods. The overall appearance of the mucosa throughout the gastric lumen, including color and texture, as well as the visibility of submucosal vessels and the structure of the gastric folds, should be examined, followed by a targeted examination of focal abnormalities *via* high-definition white light endoscopy (WLE) or image enhancement technologies. Electronic endoscopic staining accurately detects atrophic mucosa and IM, enabling "target biopsies" in areas highly suspected of IM. Narrow-band imaging (NBI), when used in conjunction with an electronic staining endoscopy, improves diagnostic accuracy and grades IM presence[52]. A real-time study revealed that compared to the conventional WLE, NBI showed a significantly heightened sensitivity in detecting IM (NBI 8% *vs* 53% for WLE; $P < 0.001$) and demonstrated a more significant diagnostic accuracy (NBI 94% *vs* WLE 83%; $P < 0.001$), especially in advanced IM stages[53]. Blue light imaging, an innovative type of optical imaging, has recently emerged and has also demonstrated equally remarkable precision in IM detection in electronic staining endoscopy. Its sensitivity and specificity in diagnosing extensive Operative Link on Gastritis IM (OLGIM III/IV) were 100% and 79%, respectively[54]. Moreover, integrating magnified endoscopy with either stained endoscopic methods or advanced image enhancement technologies may enable a deeper evaluation of the gastric mucosal architecture and minute vascular patterns.

Understanding the characteristic patterns of gastric mucosa involvement in *H. pylori* CAG and CAAG is clinically crucial. In *H. pylori* CAG, atrophic alterations often begin in the antral region and progressively spread to the upper areas, eventually encompassing the whole stomach in extreme cases. On the other hand, as autoantibodies destroy parietal cells in CAAG, the region of atrophy primarily affects the fundus and corpus of the stomach, sparing the antrum. Mucosal alterations in the initial CAAG phases tend to be inconspicuous, mainly restricted to non-specific erythema, and diagnosis is often missed without histological examination. The entire gastric corpus mucosa undergoes atrophy with the progressive depletion of parietal cells. The atrophied mucosa becomes characteristically pale, with submucosal blood vessels becoming more prominent as the gastric mucosa thins and gastric folds disappear. Upon examining the entire stomach, the corpus appeared as a flattened, slender sac adorned with small elevations (including pseudo-polyps, hyperplastic or adenomatous polyps, and NETs)[55].

Endoscopists should also recognize the endoscopic features of IM as it is an essential CAG indicator. Furthermore, NBI could help improve IM sensitivity. The IM region is often mildly nodular with cristae or tubular villous mucosa. The characteristic "pale blue crest" (a thin blue-white line on the crest of the epithelial surface) indicator, typically associated with IM, has a sensitivity and specificity of approximately 90% each. Moreover, the white opaqueness in these regions is another indicative marker for IM, albeit with a perfect specificity (100%; 95%CI: 85%-100%) but relatively low sensitivity (50%; 95%CI: 40%-50%). These white opaque areas result from microscopic lipid accumulations within the mucosa of gastric tumours and IM[56,57]. It is crucial to evaluate AG severity under endoscopy in cases where the disease was detected through endoscopic examination. Biopsies should be performed in suspected atrophic or metaplastic regions to substantiate histopathological findings and assess risk stratification. Furthermore, multiple studies endoscopically confirmed hyperplastic polyps as the most common lesions in CAG, with most polyps being < 2 cm in diameter in 10%-40% of patients and usually so multiple that they look like polyposis[55]. Endoscopists should also subject the

neighboring mucosa to biopsy to avoid a missed CAG diagnosis.

Histopathologic diagnosis: Histopathological examination is the primary method for diagnosing CAG and determining its risk for tumor complications. The updated Sydney system recommends five biopsies at standard stomach sites, as does the recent Operative link for gastritis assessment (OLGA) and an OLGIM Gastritis Evaluation System. Specifically, the process includes two biopsies each of the gastric antrum and body mucosa, and one biopsy of the gastric angle incision, followed by placing the specimens in separate specimen jars (appropriately labeled) to accurately detect the gastric mucosa and the location of their lesions[58,59]. The difference between pathological examinations is mostly determined based on whether the patient was in the prophase, progressive stage, or terminal stage of the lesion during biopsy. In CAAG, AG, which primarily affects the gastric body, and lymphocytic infiltration, which causes gastric gland injury, is the characteristic histopathological feature[60]. Based on the classification proposed by Solcia *et al*[61] and Eidt *et al*[62], the specific histopathologic changes can be divided into three developmental stages: Early, progressive and end-stage. The early stage is mainly characterized by a widely distributed inflammation within the lamina propria of the gastric mucosa, primarily centered on the fundus. Histologically, the gastric mucosa is characterized by the presence of lymphocytes (predominantly CD4+ T cells), plasma cells, eosinophils, and mast cells, as well as mild atrophy of the gastric body mucosa. In the early stage, lymphocytes containing secondary apoptotic bodies infiltrate the glands. Pseudo-hypertrophy of residual parietal cells and multiple epithelial metaplasia, may also be observed in this stage. In the progressive stage, the lamina propria exhibits a substantial aggregation of lymphocytes and plasma cells, with evident glandular atrophy and persistent early metaplasia. However, IM is usually prominent as well, and ECL cells begin to proliferate. Consequently, the original parietal cell group is replaced by a new type of hyaline, mucus-secreting epithelial cells. These characteristics are sufficient for a strong CAAG diagnosis. In the end-stage, pseudopyloric gland metaplasia and IM are widely present, manifested as the substitution of glandular structures in the stomach's fundus with fibrotic lamina propria infiltration, accompanied by microcystic changes in small crypt hyperplasia, abnormal ECL cell proliferation, type I NETs, formation of proliferative and inflammatory polyps, and low-grade or high-grade non-endocrine dysplasia or adenocarcinoma[63,64]. In *H. pylori* CAG, *H. pylori* infection also causes abundant inflammatory infiltration by several inflammatory cells, including lymphocytes, macrophages, and plasma cells. Lymphocytes are often located within lymphoid follicles, particularly those with germinal centers, which serve as a distinct marker for *H. pylori* infection. In the context of *H. pylori* gastritis, the characteristic extensive and superficial band of plasma cells in the mucosa, alongside neutrophils in the neck region, indicate active infection. This early inflammatory pattern may progress over time, ultimately causing glandular atrophy[65]. However, this inflammatory lesion develops earlier in the gastric angular notch and distal part of the stomach, and the longitudinal spread may involve the gastric body mucosa, ultimately leading to a multifocal spread of atrophic lesions, which are the basis for a potential development of neoplastic lesions [66].

Although *H. pylori* CAG and CAAG are two completely different diseases, they exhibit some overlapping features. Toh *et al*[67] discovered a molecular simulation between autoreactive antibodies targeting H+/K+ ATPase on parietal cells and *H. pylori*, and that the α-subunit of the *H. pylori*-produced urease and the α-subunit of the auto-antigenic H+/K+ ATPase share a significant sequence similarity[67,68]. Therefore, "secondary autoimmunity" may result from the antigenic mimicry between the amino acid sequence of *H. pylori* and the H+/K+ ATPase on parietal cells. Research has also demonstrated that persistent *H. pylori* infection could result in the emergence of CD4+ T cells within the stomach, which could cross-react with H+/K+ ATPase and *H. pylori*-induced antibodies in the stomach[69]. Furthermore, as previously described, in addition to being a reliable marker of gastric body mucosal damage in CAAG patients, APCA also appears in multifocal AG, implying that patients with both types of CAG have similar clinical features. Although it remains unclear whether APCA plays a significant pathogenic role in CAAG, persistent stimulation of B-lymphocytes by T-cells could result in the localized generation of APCA, leading to the hypothesis that gastric H+/K+ ATPase-responsive CD4+ T cells are a major driver in the autoimmune pathogenesis of CAAG[70]. Additionally, the interactions between increased infiltration of CD4+ T lymphocytes and gastric parietal cells with higher Fas expression, or cognate interaction amongst gastric parietal cells, could result in parietal cell apoptosis. Furthermore, the acid in the gastric antrum regulates gastrin production by G cells. In CAAG, the persistent self-attack of the gastric parietal cells creates a state of chronic acid deficiency. This disrupts the negative feedback of the gastric antrum G cells regulating gastrin secretion, thereby prompting them to continually produce gastrin, leading to hypergastrinemia, which further contributes to the development of ECL cell hyperplasia and type I gastric NETs.

Since CAG patients are at an increased risk of GC development, it is important to assess their severity. There are currently no histological reporting protocols for chronic gastritis that clinicians and patients can easily understand. Conversely, the histological reporting of hepatitis staging has good clinical utility. This prompted an international group of gastroenterologists and pathologists to develop an OLGA-OLGIM histologic staging system for inflammatory gastric diseases. This system adjusts for cancer risk and detects IM in 90% of cases[71,72]. A recent meta-analysis confirmed the significance of monitoring CAG severity based on OLGA staging to improve the detection of tumor complications in early-stage CAG patients[73]. The OLGA staging system grades gastritis from Stage 0 to Stage IV based on the severity and extent of the spread of atrophic-metaplastic changes. Multiple epidemiological studies suggested that Stages III and IV (high-risk OLGA stage) are associated with the risk of GC development. These studies also showed that *H. pylori* eradication in subjects with a high-risk OLGA stage grading does not eliminate the risk of tumor progression. Therefore, continuous monitoring of these patients, who account for < 5% of chronic gastritis cases, is recommended[74]. Nevertheless, the OLGIM staging system only considers the IM score, and its evaluation has significant drawbacks. Specifically, this staging system could undervalue atrophy assessment as it does not consider non-metaplastic atrophy and the presence of pseudopyloric metaplasia. Intestinal metaplastic cells do not cause the IM-related GC danger by themselves. According to research, IM transformation is a more widespread phenomenon caused by mucosal atrophy

transformation in the atrophic microenvironment prone to cancer[75]. Unfortunately, the practical applicability of the OLGA-OLGIM system remains limited, necessitating further implementation and promotion of the pathological grading system of CAG patients.

Despite being considered an important tool for CAG diagnosis and differential diagnosis, endoscopic techniques can only provide images of the surface of the GI mucosa. Furthermore, their diagnostic precision continues to rely on endoscopists' adherence to Standard Operating Procedures and accumulation of extensive knowledge in identifying pathologic mucosal conditions[76]. On the other hand, multipoint biopsies, although more accurate, could increase the risk of gastric injury and bleeding, and the accuracy of pathologic biopsies also depends largely on physician's experience in determining the position and depth of mucosal biopsies. Therefore, a more algorithmically focused Convolutional Neural Network was proposed[77]. This technique excels in image recognition and has emerged as a prospective examination approach in medical imaging for diagnosing CAG based on gastroscopy images, improving CAG diagnostic accuracy, and simplifying the diagnostic procedure. Nonetheless, the primary focus of this study was AG identification and diagnosis in the gastric antrum. In this regard, this study has several limitations that should be confirmed in studies with larger cohorts. Specifically, to achieve early AG treatment and delay or even reverse its progression, future research should focus on whole stomach imaging for a more comprehensive diagnosis of the entire gastric mucosal atrophy lesion. Table 1 compares the outcomes of autoimmune AG (AAG) with those of *H. pylori*-associated AG.

MANAGEMENT OF PATIENTS WITH ATROPHIC GASTRITIS: TREATMENT AND SURVEILLANCE

While numerous studies have explored the pathogenesis and clinical implications of AG, inconsistencies remain in the reported prevalence and progression rates across different populations, suggesting potential underlying factors that have yet to be fully elucidated. Moreover, there is a notable variation in the criteria used to diagnose AG, which complicates direct comparisons between studies and highlights a critical gap in the standardization of diagnostic protocols. In CAG patients who test positive for *H. pylori*, eradicating the bacteria is currently considered a top priority[78]. A retrospective study showed that eliminating *H. pylori* significantly reduced the incidence of secondary GC in individuals with mild to moderate AG over a 5.2-year follow-up period[79]. However, some studies have shown that IM may indicate the GC cascade's potential "point of no return". This indicates that even with the eradication of *H. pylori*, gastric mucosal damage cannot be reversed[80]. Consequently, early eradication of *H. pylori* should be considered before IM to prevent GC development. Identifying the most efficacious therapy for dyspeptic symptoms in CAG patients remains a subject of ongoing research. Evidence from previous studies has shown that dyspeptic symptoms in individuals with CAG lead to inhibition of stomach evacuation due to impaired gastric acid secretion, which may be caused by changes in gastric antral contraction or hypergastrinemia stimulating gastric antral contractile activity[81]. In such patients, gastric prokinetic agents may be effective. However, eradication of *H. pylori* may alleviate this symptom. Research has indicated that the positive effect of *H. pylori* eradication therapy on dyspeptic symptoms persisted for up to 12 months post-treatment in patients diagnosed with CAG[82]. PPIs are not suitable in patients with AG that invade the gastric body because the fundic glands undergo atrophic damage, impaired gastric acid secretion, and prolonged use of PPIs (more than 6 months) has been linked to the emergence of precancerous conditions in the stomach, alongside the progression of intestinal chromatoid cell hyperplasia[83]. In contrast, in patients with CAG combined with type I neuroendocrine tumors, physicians should endoscopically resect all small gNETs < 1 cm and conduct endoscopic monitoring examinations every 1 to 2 years, which may vary according to the condition of the gNETs. Surgical resection is appropriate if the gNETs are > 2 cm and have infiltrated the submucosal layer or show signs of lymph node metastasis[84,85].

If megaloblastic anemia due to vitamin B_{12} deficiency advances to pernicious anemia, the initial approach involves parenteral administration of vitamin B_{12}, followed by life-long maintenance with oral cobalamin. Oral iron supplementation may also be necessary to achieve a complete hemoglobin response[86]. In addition, studies have confirmed that vitamin B_{12} supplementation significantly reduces or prevents peripheral nervous system lesions in patients with CAG. Moreover, comparing the trends in serum vitamin B_{12} Levels and peripheral nerve conduction velocities of patients with CAG who received standard therapy without vitamin B_{12} supplementation, as well as after 1-3 and 6 months of intervention, serum vitamin B_{12} levels and nerve conduction velocities were increased after treatment[87]. Therefore, timely supplementation of vitamin B_{12} in patients with primary diseases and controlling risk factors that lead to vitamin B_{12} deficiency can reduce or prevent peripheral nervous system disorders. Given the close association of between folate, vitamin B_{12}, and homocysteine metabolic processes, it is crucial to analyze the folate status in these patients to improve the interpretation of low vitamin B_{12} Levels or high homocysteine levels.

To date, the necessity and interval of endoscopic/histological surveillance in patients with CAG has not been clarified, with some studies[88,89] suggesting that gastroscopic surveillance be considered every three years in patients with advanced CAG (stage III/IV OLGA or OLGIM); patients with advanced CAG in combination with a positive family history of GC may be more ideal for the 2-year interval, and that these surveys may improve early detection of neoplastic lesions[88-90]. In patients presenting with anti-parietal cell antibodies and/or intrinsic factor autoantibodies, iron deficiency anemia, vitamin B_{12} deficiency anemia, or serum biomarkers indicative of gastric atrophy, there is an increased risk of developing CAG[91,92]. Therefore, these patients should undergo invasive investigations at least once and have the diagnosis confirmed by histology. Table 2 compares the clinical and histological features of different stages of GA. A key limitation of this review is the absence of novel experimental findings. However, the value of this work lies in its synthesis of existing literature and its identification of research gaps that can direct future studies.

Table 1 Comparison of autoimmune atrophic gastritis and *Helicobacter pylori*-associated atrophic gastritis

Characteristic	Autoimmune atrophic gastritis	*H. pylori*-associated atrophic gastritis
Etiology	Autoimmune destruction of parietal cells[4,5]	Chronic infection by *H. pylori*[8,10]
Gastric acid secretion	Reduced, leading to hypo/achlorhydria[3]	Initially increased, but later reduced as atrophy progresses [9]
Location of atrophy	Body and fundus of the stomach[4,5]	Antrum and body of the stomach[12,43]
Serum markers	High gastrin, low pepsinogen I/II ratio, presence of antibodies against parietal cells[4,5]	Positive anti-*H. pylori* antibodies, variable pepsinogen I/II ratio[43,44]
Gastric microbiota	Altered, with decreased diversity[13,14]	Altered, often with increased colonization by non-*H. pylori* species[13,15]
Risk of gastric cancer	Increased risk, particularly for neuroendocrine tumors[36,39]	Increased risk of adenocarcinoma, particularly intestinal type[10,12]
Associated conditions	Pernicious anemia, other autoimmune diseases like thyroiditis[4,33]	Gastric ulcer, duodenal ulcer, and MALT lymphoma[6,10]

MALT: Mucosa-associated lymphoid tissue; *H. pylori: Helicobacter pylori.*

Table 2 Clinical and histological features of different stages of gastric atrophy

Stage	Clinical features	Histological features
Non-atrophic gastritis	Mild symptoms or asymptomatic[4,20]	Inflammation without glandular atrophy[4,20]
Mild atrophic gastritis	Dyspepsia, bloating, mild anemia[4,22]	Focal glandular atrophy, mild inflammation[12,43]
Moderate atrophic gastritis	More remarkable dyspepsia, iron deficiency anemia [22,25]	More extensive glandular atrophy, intestinal metaplasia may begin[4, 21]
Severe atrophic gastritis	Pernicious anemia, malabsorption symptoms[21,25]	Extensive atrophy, marked intestinal metaplasia, risk of neoplasia[12, 43]
Gastric cancer	Weight loss, abdominal pain, early satiety[26,35]	Adenocarcinoma or neuroendocrine tumor on a background of atrophy [37,39]

CONCLUSION

Despite advancements in understanding AG, significant gaps persist, particularly in the longitudinal tracking of AG progression and the role of genetic and environmental factors in influencing disease outcomes. Furthermore, the mechanisms by which AG leads to various clinical outcomes, such as its progression to GC in some patients but not others, remain poorly understood and warrant further investigation. Clinically, CAG is a multifaceted disease which presents the features of gastric atrophy, an atrophic transformation that can cause different histologic manifestations. In most patients, it is benign, however, it may progress to severe long-term health issues, including pernicious anemia or even cancer, which could pose a potentially life-threatening. Therefore, prompt and precise identification of patients with CAG are crucial for timely initiation of interventions. The clinical manifestations of CAG are nonspecific and involve multiple systemic changes, therefore its etiology may not only involve autoimmunity or *H. pylori* infection, but also unexplained anemia resulting from a lack of vitamin B_{12} and iron, autoimmune diseases, or unexplained neurological lesions. The diagnosis of CAG requires a combination of multiple serologic markers and is confirmed primarily by histopathology. Physicians should be aware that the presence of M in gastric histology typically indicates the presence of CAG. Endoscopic surveillance should be contemplated for patients with severe CAG to enable early detection of GC. However, even if recognized, endoscopic surveillance is still not well understood regarding the intervals and duration of monitoring. In addition to eradicating *H. pylori*, the treatment of CAG should also consider other treatments strategies, including monitoring deficiencies of essential micronutrients, especially iron and vitamin B_{12} deficiencies. Providing vitamin B_{12} supplements to individuals with CAG effectively alleviates symptoms of peripheral neuropathy. The most effective diagnosis and treatment approach of individuals with CAG requires persistent communication and efforts by physicians from multiple professional doctors to improve diagnosis and ensure the best treatment. Further research should explore the link between *H. pylori* infection and autoimmune disorders, aiming to establish specific diagnostic criteria for distinguishing AAG from *H. pylori*-induced multifocal AG. Such differentiation may offer valuable insights for patient management and prognosis. In addition, there is a need to integrate histological and endoscopic manifestations of CAG into a comprehensive staging system to enhance the sensitivity and specificity of cancer prediction in the future. Finally, to enhance our understanding of AG and its complex clinical manifestations, long-term, prospective, and specialized studies are needed to better define clinical syndromes related to CAG. In addition to synthesizing existing research, this review aimed to provide a comprehensive and critical analysis of the current literature on AG. By

identifying gaps in knowledge, inconsistencies in findings, and areas where further research is needed, this review contributed to advancing the field. Moreover, the review provided new perspectives on the interpretation of existing data, proposing a more integrated understanding of the histopathological and etiological aspects of AG. These insights can serve as a foundation for future experimental studies, guiding researchers in addressing the unresolved questions highlighted in this review. The integration and critical analysis of existing data presented in this review intended to facilitate a deeper understanding of AG and stimulate new lines of inquiry, ultimately contributing to the advancement of knowledge and therapeutic approaches. Future research should concentrate on large-scale, multicenter longitudinal studies that can provide a clearer picture of the natural history of AG and identify key risk factors for progression to GC. Additionally, exploring the molecular and genetic underpinnings of AG could provide new insights into its pathogenesis and potential therapeutic targets, with an emphasis on personalized medicine approaches to manage and prevent disease progression.

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FOOTNOTES

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