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STOMACH AND DUODENUM (JOSEPH PISEGNA AND JIHANE BENHAMMOU, SECTION EDITORS)

Current Perspectives in Atrophic Gastritis

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Abstract

Purpose of the Review Atrophic gastritis is a complex syndrome with gastric atrophy as a common trait. *Helicobacter pylori* infection and autoimmunity are the two main contexts in which it develops. It is slightly symptomatic, affects various aspects of general health, and remains a predisposing factor for gastric cancer. This review will update current knowledge and progress on atrophic gastritis.

Recent Findings Atrophic gastritis affects mostly adults with persistent dyspepsia, deficient anemia, autoimmunity disease, long-term proton pump inhibitor use, and a family history of gastric cancer. Gastric biopsies, expressed as Sydney system grade and OLGA/OLGIM classifications, represent the gold standard for diagnosis and cancer risk stage, respectively. Recently, electronic chromoendoscopy has allowed "targeted biopsies" of intestinal metaplasia. The associated hypochlorhydria affects the gastric microbiota composition suggesting that non-*Helicobacter pylori* microbiota may participate in the development of gastric cancer.

Summary Physicians should be aware of multifaceted clinical presentation of atrophic gastritis. It should be endoscopically monitored by targeted gastric biopsies. Autoimmune and *Helicobacter pylori*-induced atrophic gastritis are associated with different gastric microbial profiles playing different roles in gastric tumorigenesis.

Keywords Atrophic gastritis · Chromoendoscopy · Gastric cancer · Gastric microbiota · *Helicobacter pylori* · Intestinal metaplasia

Pathogenesis and Epidemiology

Atrophic gastritis (AG) is a chronic condition characterized by the replacement of the original gastric glands by intestinal metaplasia (IM), pseudopyloric metaplasia, and/or fibrosis. When AG involves the corpus oxyntic glands, impaired gastric acid and intrinsic factor secretion may lead to iron and/or vitamin B_{12} deficiency anemia as a consequence of micronutrient malabsorption [1••].

The pathogenetic mechanisms that trigger AG are still under debate. AG may arise in the context of gastric autoimmunity or as a long-term consequence of chronic *Helicobacter pylori* (*H. pylori*) infection. In autoimmune AG, the major pathogenetic role is likely played by autoreactive Th1 cytotoxic cells [2], while autoantibodies against the parietal cell H^+/K^+-ATPase proteins as "target" antigens do not seem to have a direct role [3, 4].

Over time, a long-standing *H. pylori* infection may lead to a progressive loss of gastric glands, leading to multifocal AG. *H. pylori* infection was believed to be the initial trigger in Correa's cascade leading to AG, IM, and ultimately to gastric cancer [5]. This is supported by the benefit of eradication of *H. pylori* infections on gastric cancer incidence (RR = 0.54; 95% CI 0.40 to 0.72) and gastric cancer-related mortality (RR = 0.61; 95% CI 0.40 to 0.92) in healthy individuals [6], as well as on a decrease in AG and, to a minor extent, IM severity scores [7].

In late-stage disease, the pathogenetic definition of AG may often be difficult. *H. pylori* might have been cured by eradication treatment or disappeared due to the progression of oxyntic mucosa atrophy. The diagnosis of autoimmune AG essentially relies on a spared antral mucosa and positivity against parietal cell autoantibodies [8]. However, concomitant *H. pylori* infection may lead to inflamed antral mucosa in autoimmune AG, and parietal cell autoantibodies are often retrieved in *H. pylori*-related AG, probably representing a

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marker of oxyntic mucosa damage rather than an exclusive clue of gastric autoimmunity [1, 9, 10]. Additionally, the clinical features of *H. pylori*-related and autoimmune AG may overlap. Dyspeptic symptoms, vitamin B_{12} and/or iron deficiency anemia, and autoimmune disorders, in particular autoimmune thyroid disease, may occur in both types of AG [11–13], thus excluding them as distinctive clinical clues.

Patients with *H. pylori*-related and autoimmune AG are at increased risk for gastric neoplasias, intestinal-type adenocarcinoma, and type 1 gastric neuroendocrine tumors [1, 5, 8, 14], probably in relation to the natural history of the disease in the individual patient. In most patients, however, the exact onset of oxyntic mucosa destruction remains unknown due to its slow and gradual course. Whether a clear-cut distinction between autoimmune and *H. pylori* AG is useful with regard to the management and/or outcome of the patient remains to be established.

The prevalence of AG is different based on the diagnostic test used, as shown in a systematic review [15]: the biopsy-based prevalence was 33.4% and 31.6% in the general population and in selected clinical settings, respectively, while the serology-based prevalence was 23.9% and 27.0% in the same populations. The incidences per year were highly variable, ranging from 0 to 10.9%, as reported by another systematic review [16], likely related to differences in the study populations, in particular with regard to the intragastric localization of AG: in the antrum, in the corpus, or both.

Noninvasive and Invasive Diagnoses

The gold standard for the diagnosis of AG is the histopathological evaluation of gastric antrum and corpus biopsies [1, 17]. Nevertheless, serology tests may be helpful in identifying subjects at risk for AG [18, 19]. The serological assessment of gastrin-17 and pepsinogens allows us to screen patients to identify those needing gastroscopy to confirm the diagnosis. The presence of antral AG may be suspected when the gastrin values are low, and the presence of AG of the corpus may be suspected when gastrin values are high. When pepsinogen I and/or the pepsinogen I/II ratio are low, corpus AG may be present [20]. The assessment of antibodies against *H. pylori* may be helpful in diagnosing an active or previous *H. pylori* infection [18].

A meta-analysis reported a sensitivity and specificity of 69% (95% CI 55–80%) and 88% (95% CI 77–94%), respectively, for pepsinogens in AG patients [21], including heterogeneous studies for different analytical methods and cutoff values for pepsinogens [22]. Another meta-analysis on AG patients showed a relatively poor diagnostic performance of gastrin-17 with a sensitivity and specificity of 48% (95% CI 45–51%) and 79% (95% CI 77–81%), respectively [23]. A lower diagnostic performance of gastrin-17 was reported in patients with *H. pylori*-related AG (AUC = 0.62) (AUC = 0.83) than in those with autoimmune AG [24]. A recent meta-analysis reported a sensitivity of 74.7% (95% CI 62–84.3%) and a specificity of 95.6% (95% CI 92.6–97.4%) of a panel test including pepsinogens I and II, gastrin-17, and anti-*H. pylori* antibodies [25]. These meta-analyses have some pitfalls in the form of the low methodological quality and high heterogeneity of the retrieved studies. Parietal cell autoantibodies represent another promising tool for the noninvasive diagnosis of autoimmune AG [26, 27] and *H. pylori*-related AG, particularly against the single subunits of H+/K+-ATPase [9, 28].

Notwithstanding the gold standard of histopathological assessment of biopsies for AG diagnosis [17], in Japan and in other Eastern countries, AG diagnosis mainly relies on the endoscopic classification by Kimura-Takemoto [29], while gastric biopsies are obtained only when IM is suspected. According to this classification, when an atrophic border remains on the lesser curvature, it is called closed-type AG, and when the AG spreads onto the anterior and posterior walls of the stomach without an atrophic border, it is called open-type AG; these two main types are further divided into three severity classes [29]. The Kimura-Takemoto classification originated from *H. pylori* AG, where atrophic damage begins in the antral mucosa and spreads proximally to the corpus along the lesser curvature [29]. The Kyoto global consensus report on *H. pylori* gastritis states that after appropriate training, atrophic mucosa and intestinal metaplasia can be accurately detected by image-enhanced endoscopy (strong grade of recommendation, high evidence level, consensus level 84.2%) [19]. In the Western world, gastrointestinal endoscopists are generally not familiar with the Kimura-Takemoto classification, and interobserver reliability is low; this may also be due to the higher prevalence of autoimmune AG, which does not fit with the classification because the antrum mucosa is spared by definition [30].

Western endoscopists instead prefer to take two biopsies of the antrum and two of the corpus and send them in separate vials to achieve a correct staging of AG and/or IM, according to the European MAPS II guidelines [31••]. A further biopsy from the incisura may be taken (to be sent in the same vial as the antrum biopsies) following the updated Sydney system and for staging according to OLGA/OLGIM classifications [17, 32–34].

In recent years, electronic or virtual chromoendoscopy has gained increasing attention in the diagnosis of AG, as it allows target biopsies to be obtained in gastric areas in which the presence of IM is endoscopically suspected [35]. A real-time study reported greater diagnostic accuracy (94% vs 83%, $p < 0.001$) and a higher sensitivity for the presence of IM (87% vs 53%, $p < 0.001$) with narrow-band imaging (NBI) chromoendoscopy than with traditional white-light endoscopy (WLE) [36]. A new classification for the endoscopic grading of gastric intestinal metaplasia (EGGIM) was reported and validated, which, compared with histopathology, was shown

to accurately stage extensive IM (OLGIM III/IV) (sensitivity 89.4% at a specificity of 94.6%) for the diagnosis of AG [37]. Another type of electronic chromoendoscopy, blue light imaging (BLI), was developed more recently and showed a higher (100%) sensitivity at a lower (79%) specificity for extensive IM (OLGIM III/IV) than NBI [38]. In another study, a concordance between BLI endoscopic classification and histology of 93% for the antrum and 88% for the corpus was reported, showing a positive and negative predictive value for atrophy of 0.63 and 0.97 and for IM of 0.74 and 0.83, respectively [39]. Figure 1 shows endoscopic pictures of the gastric corpus mucosa of an AG patient obtained by traditional WLE and NBI gastroscopy.

Clinical Presentations

AG is prevalent in many parts of the world with large variations and may affect individuals of all ages, albeit it is more common among older adults [1••]. Serological studies and a histological study have shown an increased prevalence of AG with increasing age [40–42]. When compared with individuals aged less than 40 years, those aged over 40 presented with AG twice as often [41]. In Sweden, an unexpected age trend with an increasing prevalence of AG in adults aged 35–44 years but a decreasing prevalence in those aged 55–64 years has been reported [43].

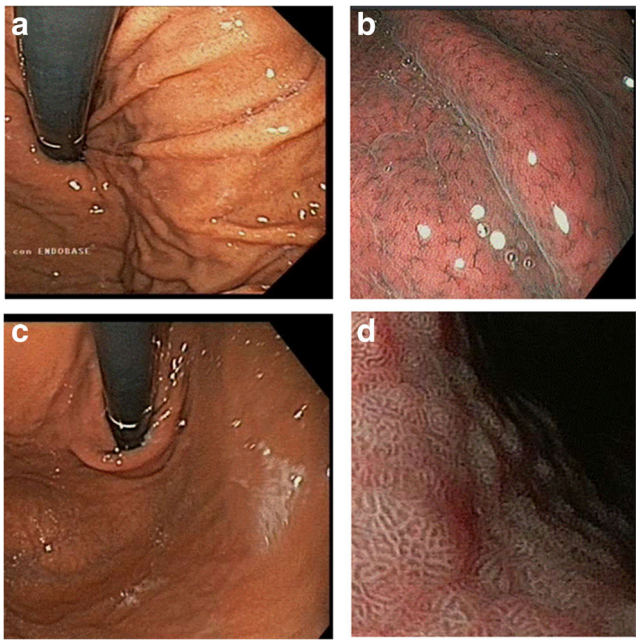

Fig. 1 Endoscopic images of atrophic gastritis by white-light and narrow-band imaging chromoendoscopy. **a** Normal gastric folds of the corpus-fundus at retroflexed traditional white-light gastroscopy of a healthy stomach. **b** Normal gastric mucosa at narrow-band imaging chromoendoscopy: regular and circular mucosal pattern with regular peripheral vessels. **c** Loss of folded pattern of corpus mucosa with prominent vascular profile of corpus-fundus at retroflexed traditional white-light gastroscopy of atrophic stomach. **d** Intestinal metaplasia at narrow-band imaging chromoendoscopy in atrophic gastritis: regular vessels with tubular glands with light blue crests

When AG involves the corpus mucosa, over time, malabsorption of vitamin B_{12} and iron may result in hematological alterations such as anemia, isolated mean cell volume alterations (macro- or microcytosis), anisocytosis, dimorphic anemia, and pancytopenia [1, 13, 44]. AG was diagnosed in 37.5% of patients with macrocytic anemia and in 19.5% of those with microcytic anemia; AG patients with macrocytic anemia were approximately 20 years older than those with microcytic anemia [45].

Macrocytic anemia due to vitamin B_{12} (cobalamin) malabsorption secondary to intrinsic factor deficiency, itself arising from atrophy of the gastric parietal cells, is called pernicious anemia [1, 44, 45] and is not only a manifestation of autoimmune atrophic gastritis [1••]. Iron deficiency anemia arises due to iron malabsorption as a consequence of impaired gastric acid secretion; it may be associated with low or normal vitamin B_{12} levels [46].

AG may be the only cause of refractory iron deficiency anemia [48], and iron deficiency anemia may precede the onset of pernicious anemia in 35–58% of AG patients [46]. Approximately half of newly diagnosed AG patients present with iron deficiency anemia, likely representing the most frequent hematological alteration of this condition [47].

Deficiencies in both micronutrients, in addition to hematological alterations, may lead to potentially irreversible neurological and psychiatric alterations [48–51]. Increased homocysteine, which is linked to an increased risk for thromboembolism and cardiovascular disease, is associated with vitamin B_{12} deficiency [52] and may be considered an underhand clinical clue for undiagnosed AG [53–55]. Thus, in particular, in elderly individuals with age-related frailty and who commonly present with cardiological and neurological comorbidities, a timely diagnosis of AG and its eventually triggered and treatable micronutrient deficiencies is crucial for outcome and quality of life.

Some studies have reported gastrointestinal symptoms in AG patients, traditionally considered a symptomless disorder. In a multicenter study on patients with upper gastrointestinal symptoms, AG was diagnosed by biopsy in 30.1% of patients [12]. In patients with autoimmune AG, gastrointestinal symptoms were present in 56.7%, the most common of which were early satiety and postprandial fullness [56]. In heavy contrast with the reduced gastric acid secretion present in AG, gastroesophageal reflux symptoms, such as regurgitation and heartburn, were reported in nearly 25% of patients with this condition [57, 58]. Reflux and dyspeptic symptoms were similarly associated in patients with and without AG, thus excluding the first one as pre-endoscopic clues for ruling out AG, while postprandial fullness was reported as a clinical predictor for autoimmune AG [12]. Thus, in patients with persistent, long-

standing, uninvestigated upper gastrointestinal symptoms, gastroscopy with biopsy should be performed to rule out the eventual presence of AG. Following current recommendations, dyspeptic patients younger than 50–55 years of age are rarely referred for gastroscopy, and functional dyspepsia is often diagnosed on a clinical basis only [1, 59], possibly overlooking AG.

A solid body of evidence shows that long-term use of proton pump inhibitors (PPIs) is potentially able to induce or at least worsen the corpus-involving AG in *H. pylori*-infected patients [60–63]. An increased risk of gastric cancer has been shown in *H. pylori*-positive subjects on long-term PPI treatment [62]. A meta-analysis showed a moderately higher prevalence of AG in long-term PPI users than in controls (15.8% vs 13.3%, OR 1.5, 95% CI 1.0–2.4) [63]. An increased risk of AG was confirmed in first-degree relatives of subjects with *H. pylori* infection and/or gastric cancer in some studies [63, 64] but dismissed in others [65, 66].

A meta-analysis showed a higher risk for *H. pylori* infection and AG in first-degree relatives of patients with gastric cancer [67]. In individuals with a family history of precancerous conditions and gastric cancer, a higher incidence of gastric cancer was reported; a positive family history of any precancerous changes and gastric cancer was associated with a 2.5-fold and a 3.8-fold increase in the gastric cancer (noncardia) hazard ratios, respectively, over those of the relatives of index persons with normal or less significant mucosal changes [68]. A positive family history of first-degree relatives of gastric cancer, the absence of duodenal ulcers, and older age were independent risk factors for the development of AG among *H. pylori*-positive patients assessed by endoscopy in a Japanese study on *H. pylori*-positive patients [69].

Some autoimmune conditions may be associated with AG, not only with autoimmune AG but also with *H. pylori* AG [1, 70, 71].

Autoimmune thyroid disease, in particular Hashimoto's thyroiditis, is the most frequently associated autoimmune comorbidity [71, 72]. The term "thyrogastric syndrome" was coined to indicate both conditions present in the same subject [71, 72]. Subjects with autoimmune thyroid disease and/or type 1 diabetes seem to have an up to 5-fold increased risk of autoimmune AG. This association has been described in series from different regions throughout the world and thus seems independent of ethnicity [13, 72]. A cross-sectional study reported that 53% of autoimmune and non-autoimmune AG patients had an associated thyroid disease (autoimmune in 75.7%) and half of them were unaware of it. AG and autoimmune thyroid disease often occur together, supporting an active case-finding strategy to rule out occult autoimmune thyroid disease in both autoimmune and non-autoimmune AG patients [71].

The main clinical presentations eventually hiding the presence of AG comprise unexplained iron deficiency anemia, macrocytic anemia or isolated macrocytosis, long-standing uninvestigated dyspepsia, autoimmune thyroid disease and type 1 diabetes mellitus, long-term continuous PPI treatment, and a positive family history of gastric cancer and/or precancerous lesions. To these highly clinically suspicious subjects, an upper gastrointestinal endoscopy with a standard biopsy protocol, possibly with NBI or BLE chromoendoscopy, should be offered to diagnose or rule out the presence of AG.

Clinical and Endoscopic Management

Clinical and endoscopic management of patients with AG aims at relieving symptoms, treating and restoring micronutrient deficiencies and curing *H. pylori* infection when present, and preventing neoplastic complications by appropriate endoscopic surveillance [73].

The most common gastrointestinal symptoms in AG are related to dyspepsia, mainly early satiety or postprandial fullness. When atrophic damage involves the corpus oxyntic glands with consequent impaired gastric acid secretion, proton pump inhibitors are not indicated [74]. A study on patients with autoimmune AG and gastroesophageal reflux symptoms showed that proton pump inhibitors were not useful for relieving symptoms because of the nonacidic nature of the reflux [58]. As shown in a systematic review performed to assess the progression of gastric precancerous conditions (AG, IM, enterochromaffin-like cell hyperplasia, dysplasia), the long-term use of proton pump inhibitors (>6 months) worsened enterochromaffin-like cell hyperplasia, although progression of AG or IM was not observed [75].

From a physiopathological point of view, dyspepsia in AG may be linked to delayed gastric emptying, itself related to reduced gastric acid secretion [76]. Thus, theoretically, prokinetics might be useful for relieving dyspeptic symptoms in AG, although studies proving their efficacy are lacking.

To date, at least two studies have provided evidence that in AG patients, the most effective therapy for dyspeptic symptoms is the curing of *H. pylori* infection [77, 78].

The proactive search for active *H. pylori* infections and their curing plays an important role in the management of AG patients due to the relationship between the organism and the increased gastric cancer risk. The type I gastric carcinogen *H. pylori* [79] is associated with a 3- to 6-fold increased risk of developing gastric cancer in colonized subjects [19], and its eradication significantly reduces this risk (RR 0.56, 95% CI =0.48–0.66) [80]. *H. pylori*-related chronic inflammation may evolve into AG and IM, which represent precancerous conditions predisposing patients to the development of gastric cancer, as hypothesized by Correa [5, 81]. The curing of *H. pylori* may slow this process and may sometimes even lead to a regression of these conditions, particularly in patients without IM [7, 81].

Noninvasive tests for the diagnosis of an *H. pylori* infection, such as the urea breath test or stool antigen test, may give false negative results in corpus-involving AG patients because these tests rely on intragastric pH and bacterial load [82]. Therefore, in AG patients, the diagnosis of active *H. pylori* infections should be based upon the histopathology of gastric biopsies and/or serology (IgG *H. pylori* antibodies).

According to the MAPS II guidelines [31••], patients with AG should be offered endoscopic surveillance depending on the intragastric locations of the AG and IM and risk stratification. Endoscopic surveillance (as well as diagnosis) of AG, when available and after proper training, should be performed with high-definition electronic chromoendoscopy to then perform targeted biopsies of irregular areas [31••]. When AG and/or IM involves the gastric corpus and antrum (extensive AG/IM), surveillance should be scheduled every 3 years or every 1–2 years if a first-degree family history of gastric cancer is present. When AG and/or IM involves the corpus only (autoimmune AG), surveillance should be scheduled every 3 years; when AG with IM involves the antrum only, surveillance should be scheduled every 3 years when a first-degree family history of gastric cancer, incomplete IM, or persistent *H. pylori* infection is concomitantly present. Patients with antrum AG without IM do not need any surveillance [31••].

In extensive AG, the 3-year interval of surveillance has been shown to be cost-effective in patients at intermediate and low risk for gastric cancer [83, 84]. However, the occurrence of gastric neoplastic lesions has been observed in follow-up studies at 2-year intervals [33, 85] and in low-risk stages of OLGA/OLGIM [14, 34, 86, 87], strengthening the need for further studies to assess the optimal time interval and high-risk groups of AG patients to prevent gastric cancer.

AG is linked to an increased risk of type 1 neuroendocrine tumors and gastrin-dependent, well-differentiated neoplasms with generally benign behavior [1••]. These tumors are strongly associated with autoimmune AG but may also occur in *H. pylori*-related AG [1, 14], and AG patients with type 1 gastric neuroendocrine tumors are at higher risk of developing metachronous gastric cancer [88]. To date, no specific surveillance protocol for gastric neuroendocrine tumors is available. Endoscopic surveillance of gastric cancer and dysplasia according to the MAPS II guidelines is therefore concomitantly helpful in the early detection of type 1 neuroendocrine tumors.

Atrophic Gastritis and Gastric Microbiota

The gastric environment is characterized by a defensive acid barrier that protects against orally ingested microorganisms, which leads to their inactivation before reaching the intestine [89]. The progressive loss of oxyntic mucosa due to a variety of pathological mechanisms is a common feature found in *H. pylori*-related and autoimmune AG [1••]. The loss of acid-secreting parietal cells leads to hypochlorhydria, which breaks down the bactericidal acid barrier with a potentially subsequent overgrowth of bacteria other than *H. pylori*.

The gastric microbiota has been increasingly investigated in recent years as a result of the development of molecular-based methods [90••].

H. pylori is the best known but certainly not the only component of the gastric microbiota. *H. pylori*, a member of the Proteobacteria phylum, was classified as a class I carcinogen by the World Health Organization [79]. Inflammation and mucosal atrophy induced by *H. pylori* may cause host gene damage, resulting in genetic instability, dysplasia, and eventually gastric cancer [81]. While the pathogenic mechanism of *H. pylori* has been sufficiently clarified, the potential carcinogenic mechanisms of non-*H. pylori* bacteria are under debate; they may include intensifying gastric mucosa inflammation, altering the host immune system, or contributing to the conversion of dietary nitrates in carcinogens such as nitric oxide and N-nitrosamines [91]. From current knowledge, the healthy gastric microbiota consists of Proteobacteria, Firmicutes, Bacteroidetes, and Fusobacteria, while other phyla are less frequently encountered [92]. Dysbiosis in the stomach may potentially have a role in the multifactorial etiopathogenesis of gastric carcinogenesis;

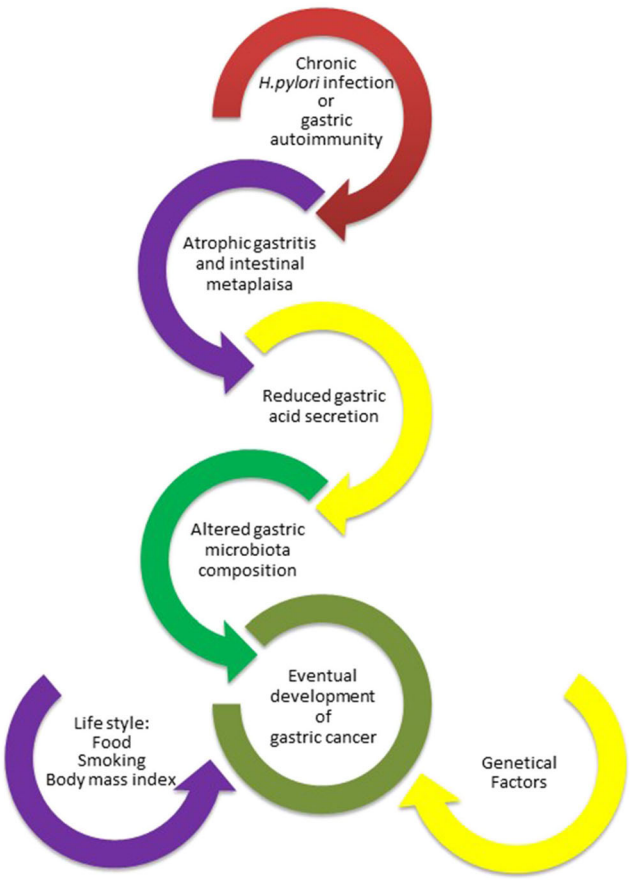

Fig. 2 Relationship between atrophic gastritis, gastric microbiota, and gastric cancer

nevertheless, no consensus in this field has been reached [93–95]. Figure 2 shows the supposed relationship between atrophic gastritis, gastric microbiota, and gastric cancer.

In recent years, some studies aiming to compare healthy stomachs with *H. pylori* gastritis/atrophic gastritis or gastric cancer have been performed to better understand whether progressive changes in gastric microbiota could be associated with the progression of gastric carcinogenesis. Most cases of gastric cancer develop in the presence of precancerous conditions such as AG. Conflicting data regarding significant differences among AG and gastric cancer microbiota are reported in the literature: some studies have described a lower gastric microbial diversity possibly associated with AG and GC, while other papers have not confirmed this result [90••]. Most studies have shown that the gastric cancer microbiota seems to be characterized by a decreased presence of *H. pylori* and a contemporary enrichment of oral taxa such as Lactococcus, Bacillus, Prevotella, Veillonella, and Leptotrichia as well as intestinal taxa such as Lactobacillus, Streptococcaceae, Staphylococcus, Clostridium, and Fusobacterium; however, heterogeneous profiles have been found in other studies, such as the decrease in Streptococcus in individuals with gastric cancer reported in a Portuguese cohort study [92, 94, 96]. Furthermore, a British study focusing on different hypochlorhydric states showed that the gastric microbiota of *H. pylori*-induced AG patients was characterized by a lower bacterial diversity with a prevalence of Proteobacteria (as *Helicobacter* itself is a member of this phylum), whereas autoimmune AG resulted in a greater bacterial abundance, with the largest proportion of Streptococci among the groups investigated [97••]. Research in this field is therefore at an early stage; longitudinal studies on the gastric microbiota changes underlying the progression of the different disease forms, including *H. pylori* gastritis, *H. pylori*-related and autoimmune AG, and gastric cancer, are awaited [98].

Concluding Remarks

Physicians of different specialties should be aware of AG and its multifaceted clinical presentation. Once a diagnosis of AG is established, gastric biopsies performed during surveillance endoscopy should be limited to suspected target areas. Autoimmune and *H. pylori*-induced AG are associated with different gastric microbial profiles that may play a role in gastric tumorigenesis.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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