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Autoimmune Gastritis: Unveiling the Mystery

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Atrophic gastritis is primarily caused by *Helicobacter pylori* infection and autoimmune mechanisms. In South Korea, where *H. pylori* infections remain highly prevalent, standardized guidelines for the use of serological testing or biopsies for diagnosing autoimmune gastritis (AIG) have not been developed. Recently, as *H. pylori* infection rates have declined and trends associated with gastric cancer and gastric neuroendocrine neoplasms (gNENs) have shifted, interest in AIG has increased, particularly in Asia. However, AIG diagnoses are often delayed owing to a lack of suspicion; even when AIG is considered, the limited understanding of the disease hampers its accurate diagnosis. Furthermore, the absence of established treatments and standardized follow-up protocols pose significant challenges for patient management. The loss of gastric acid secretion, a critical component of digestive function, and destruction of the gastric corpus mucosa are caused by autoimmune mechanisms, leading to incomplete protein digestion, micronutrient deficiencies, gut microbiota imbalances, and elevated gastrin levels that eventually contribute to neoplastic lesions, such as gNENs and gastric cancer. Although AIG is an immune-related gastrointestinal disorder, it intersects with various disciplines, including pathology, genetics, microbiology, endocrinology, hematology, and oncology, and many unresolved issues remain in these areas. Research to address unanswered questions about the disease pathogenesis, the relationship between AIG and *H. pylori*, appropriate diagnostic methods and the risk of gastric neoplasms has previously been published. This review provides an overview of the current findings and explores unanswered questions surrounding AIG to help elucidate its complex pathogenesis, clinical implications, and potential management strategies.

Keywords Autoimmune diseases; Gastric parietal cells; Gastritis; *Helicobacter pylori*; Stomach neoplasms.

INTRODUCTION

The primary causes of chronic atrophic gastritis, a preneoplastic condition, include *Helicobacter pylori* infection and autoimmune gastritis (AIG) that arises from host immune dysregulation.[1,2] AIG is characterized by epithelial cell damage and hypo- or achlorhydria, resulting from apoptosis of parietal cells in the gastric body. AIG is known to contribute to the development of neoplastic lesions, including gastric neuroendocrine neoplasms (gNENs).[3] Although the prevalence of *H. pylori* infections is decreasing, recent years have seen a rise in the number of gastric cancer cases among women under 50 years of age and an increasing incidence of gNENs; this is driving a greater interest in AIG.[4,5] Notably, the number of studies on AIG has grown significantly since 2018, with more than half of the existing literature published within the past decade. Research output has been particularly prominent in Asia, including Japan and China.[6] Authors based in South Korea have also contributed several case studies and original research articles regarding AIG.[7-11] Despite this growing body of work, many aspects of AIG remain unresolved or controversial, including its pathogenesis, the influence of *H. pylori* in-

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fection, diagnostic methods, the role of autoantibodies, and the risk of gastric cancer associated with AIG. The diagnostic criteria and follow-up protocols for AIG have also not been standardized, to date.[12] This review summarizes the current findings and explores unanswered questions regarding AIG, addressing its complex pathogenesis, clinical implications, and potential management strategies.

PATHOGENESIS AND PROGRESSION OF AIG

AIG is an immune-mediated disease that targets the parietal cells of the gastric body and is characterized by uncontrolled self-regulation. The disease is more common in Western than in Asian populations.[13,14] Although its prevalence in the general population is estimated to be between 0.1% and 2%, variations in diagnostic methods make the exact rate uncertain.[15] The characteristic pathogenic feature of AIG is the recognition of the H^+/K^+ adenosine triphosphatase (ATPase) proton pump, expressed on parietal cells, as an autoantigen by anti-parietal cell antibodies (PCAs).[16] PCAs are produced when autoreactive T cells cause parietal cell damage, exposing the molecular pattern of the H^+/K^+ ATPases. These antibodies induce complement-dependent cytotoxicity, which contributes to gastric mucosal damage. However, PCAs are not found in all patients with AIG, and they are believed to have a low likelihood of directly inducing parietal cell apoptosis.[3,17] The pathogenesis of parietal cell destruction primarily involves cell-mediated immune responses, with the autoreactivity of $CD4^+$ helper T1 (Th1) cells playing a significant role. Parietal cells expressing major histocompatibility complex (MHC) class II molecules activate $CD4^+$ Th1 cells, which secrete pro-inflammatory cytokines, such as tumor necrosis factor (TNF), interferon-γ (IFN-γ), and interleukin-2 (IL-2). The autoreactivity of $CD4^+$ Th1 cells induces proliferation of $CD8^+$ cytotoxic T cells and triggers Fas–Fas ligand pathway-mediated apoptosis and perforin-mediated cytotoxicity in parietal cells.[18] Activated B cells and plasma cells produce autoantibodies whereas macrophages and mast cells secrete IL-13, leading to atrophy of the oxyntic mucosa and intraepithelial metaplasia.[3,19] Fig. 1 provides a schematic overview of the pathogenetic interactions occurring in AIG.[3] A recent study has described the infiltration of the lamina propria by $CD45^+$ and $CD38^+$ mononuclear cells; the elevated presence of various cytokines, including TNF, transforming growth factor-β (TGF-β), IL-15, and the metabokine mucosal nicotinamide phosphoribosyl transferase; and the overexpression of thymic stromal lymphopoietin receptor in the gastric mucosa of patients with AIG.[20] Research is ongoing to explore the potential therapeutic impact of modulating these cytokines and factors.[17]

AIG progression occurs in two stages: the inflammatory reaction stage (non-atrophic stage) and the atrophic stage.[21] During the inflammatory reaction stage, PCAs are detectable in the serum, but histological evidence of atrophy or epithelial metaplasia is absent; this state is termed "potential AIG." About 50% of potential AIG cases progress to overt AIG within two

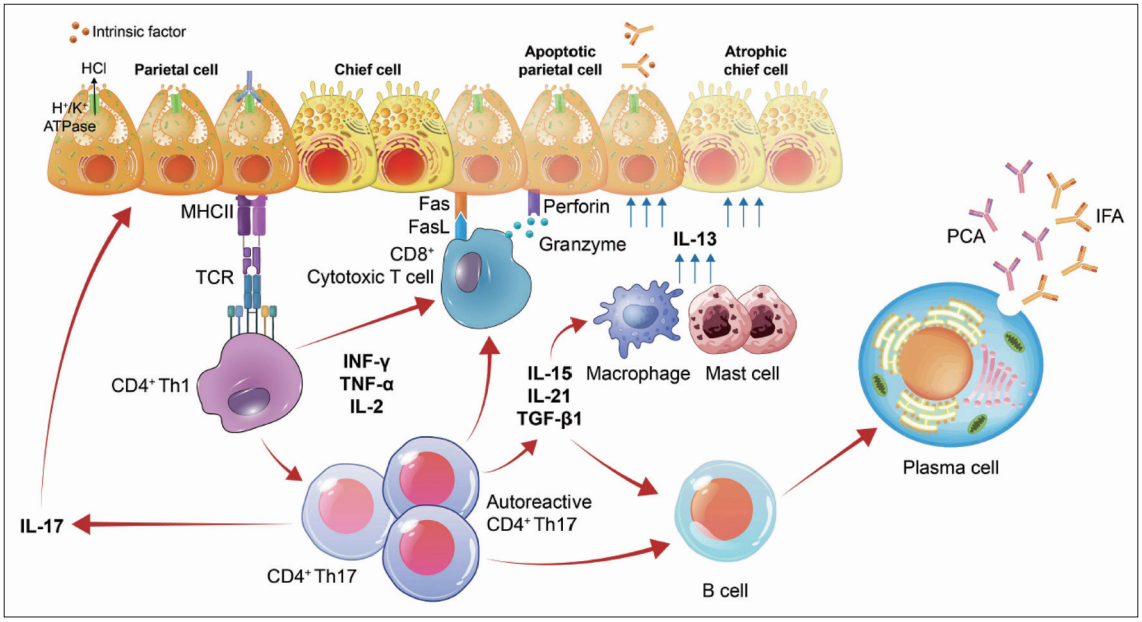

Fig. 1. Pathogenetic interactions in autoimmune gastritis. This figure has been reproduced from Lenti et al. Nat Rev Dis Primers 2020;6:56.[3], with permission of the Springer Nature. HCl, hydrogen chloride; ATPase, adenosine triphosphatase; MHC II, major histocompatibility complex class II; TCR, T cell receptor; FasL, Fas ligand; CD, cluster of differentiation; Th, helper T cell; IFN, interferon; TNF, tumor necrosis factor; IL, interleukin; TGF, tumor growth factor; PCA, anti-parietal cell antibody; IFA, intrinsic factor antibody.

years, particularly in patients who have other, concurrent autoimmune diseases, such as autoimmune thyroid disease, type 1 diabetes, vitiligo, or celiac disease.[22] However, whether all patients with PCAs progress to overt AIG remains unclear. Moreover, whether this observation is due to an actual lack of progression or due to slow progression is unknown. Thus, further prospective studies into the underlying pathophysiology are warranted. In the potential AIG stage, increased $CD3^+$ intraepithelial lymphocytes (IELs) have been identified in the lamina propria of the oxyntic gland mucosa.[23] $CD3^+$ IELs are lymphocytes associated with mucosal damage and are known to influence the tumor microenvironment in the serrated neoplastic pathway and in colorectal cancer.[24,25] The presence of IELs may serve as a marker for early AIG, including potential AIG. However, IEL infiltration is also observed in gastritis arising from other immune disorders, such as type 1 diabetes, systemic lupus erythematosus, primary biliary cirrhosis, autoimmune hepatitis, and Sjögren syndrome, as well as in the absence of *H. pylori* infection.[26] Thus, additional research on the role and function of IELs in potential AIG is needed.

The atrophic stage, referred to as "overt AIG," ranges from early-stage AIG, characterized by lymphocyte and plasma cell infiltration with mild atrophy of the oxyntic gland mucosa, to end-stage AIG, marked by severe atrophy and epithelial metaplasia. In patients with end-stage AIG, neoplastic lesions, such as enterochromaffin-like (ECL) cell dysplasia, gNENs, and intraepithelial dysplasia, may develop.[27] Moreover, histological recovery or regression does not occur, and tissue damage is most pronounced during the first two years after diagnosis, with progression being more rapid during the early than during the end stage. Women have been shown to have a higher incidence of AIG, but neoplastic complications during the end stage are more likely to occur in men.[28] The reasons for this sex disparity remain unclear.

THE ROLE OF *H. PYLORI* IN AIG

The relationship between *H. pylori* infection and AIG remains unclear, but damage to the oxyntic gland mucosa caused by the infection likely influences the onset and progression of AIG. A range of mechanisms have been proposed to explain the pathogenesis of AIG, including the molecular mimicry hypothesis. According to this hypothesis, *H. pylori*'s major surface protein, β-urease, shares over 70% sequence homology with the β subunit of the H^+/K^+ ATPase, potentially inducing $CD4^+$ Th1 cell autoreactivity in response to these peptides and triggering autoimmune responses.[29] Additionally, *H. pylori* infection has been reported to expose MHC class II molecules on gastric epithelial cells, enhancing their antigen-presenting capability and initiating autoimmune reactions mediated by $CD4^+$ Th1 cells.[30]

Interestingly, recent case studies and other research have suggested that *H. pylori* infection may inhibit AIG development. Cases have been reported where AIG was diagnosed after *H. pylori* eradication, as evidenced by the development of corpus-dominant atrophic gastritis and the presence of autoantibodies.[31,32] Whether eradication therapy activates AIG or whether this sequence represents the natural course of the disease remains unclear. The inflammatory processes in the gastric mucosa are strongly influenced by the balance between Th1 and helper T2 (Th2) immune responses.[33] In an animal study using mice with induced AIG mice, the Th2 immune response and TGF-β response induced by *H. pylori* infection were shown to suppress the manifestation of the disease induced by the Th1 immune response to AIG.[34] A significant reduction in regulatory T cells (Tregs) following eradication therapy may lead to a decrease in the immunosuppressive effect of Tregs,[35] potentially inducing the Th1 immune response observed in AIG. A multicenter cohort study analyzing the potential role of *H. pylori* in AIG found more typical features of autoimmune disease and higher serum gastrin levels in patients with AIG without *H. pylori* infection than in those with infection.[36] These findings suggested that AIG is more strongly associated with family history and other autoimmune conditions than with *H. pylori* infection. Moreover, tissue damage tended to be more severe in *H. pylori*-negative patients with AIG.

Given that *H. pylori* infection and AIG may independently affect the gastric mucosa, through different mechanisms, additional molecular biology and prospective longitudinal research studies are necessary to elucidate the differences in mucosal environment changes and tissue damage associated with each condition.

DIAGNOSTIC METHODS AND CRITERIA

AIG is diagnosed using endoscopy and separately obtained biopsy specimens from the gastric body and pyloric antrum, with the most sensitive serological test being detection of PCAs.[15] However, no standardized diagnostic criteria currently exist. In the West, diagnoses have been based on the characteristics of histological findings in the gastric body and pyloric antrum, including destruction or disappearance of parietal cells, pseudopyloric or intestinal metaplasia (IM), ECL cell hyperplasia in the gastric body, and gastrin cell hyperplasia in the pyloric antrum.[28,36] In 2023, the Japanese Society of Gastroenterology proposed diagnostic criteria for AIG that included characteristic endoscopic findings, autoantibodies (PCAs and/or in-

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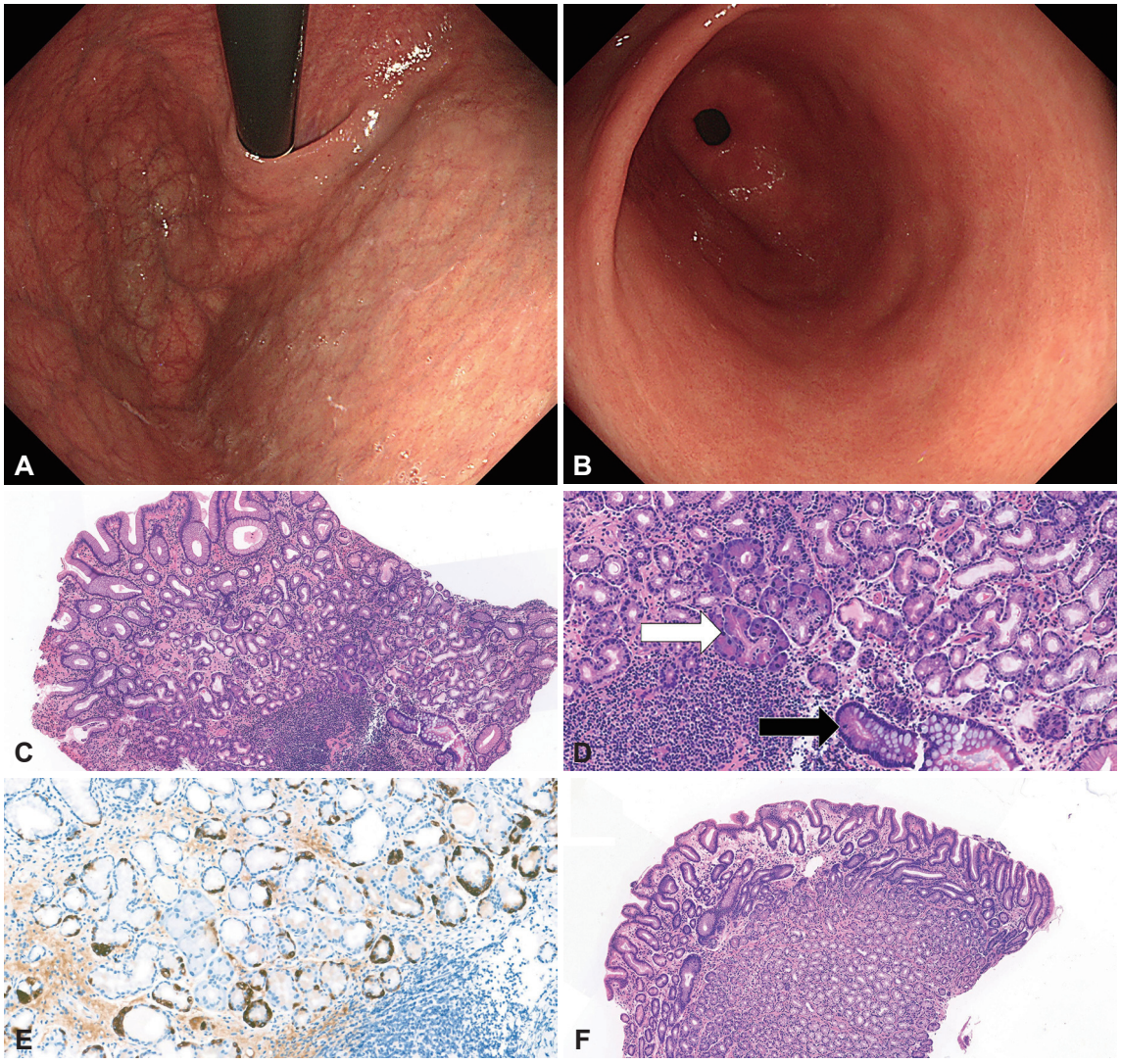

Fig. 2. Sixty-three-year-old woman with autoimmune gastritis, florid stage. Blood test results were as follows: pepsinogen I, 8.3 ng/mL; pepsinogen II, 12.3 ng/mL; pepsinogen I/II ratio, 0.7; serum gastrin, >1000 pg/mL; *Helicobacter pylori* antibody (IgG), equivocal; anti-parietal cell antibody, positive (1:80). A: The fundic mucosa is diffusely atrophic. B: The antral mucosa appears relatively normal. No endoscopic evidence of atrophy is seen (case and endoscopic images courtesy of Professor Jun Haeng Lee from the Department of Medicine at Sungkyunkwan University School of Medicine, Samsung Medical Center). C: The corporal mucosa shows extensive loss of oxyntic glands and lymphoplasmacytic infiltrates in the deeper portion of the mucosa (hematoxylin and eosin [H&E] staining, 4×). D: The atrophic corporal mucosa has been replaced by pyloric metaplasia, pancreatic metaplasia (white arrow), and intestinal metaplasia (black arrow) (H&E staining, 10×). E: Chromogranin immunohistochemistry demonstrates enterochromaffin-like cell hyperplasia (10×). F: The antral mucosa appears normal (H&E staining, 4×) (histological images courtesy of Professor Soomin Ahn from the Department of Pathology and Translational Genomics at Sungkyunkwan University School of Medicine, Samsung Medical Center).

trinsic factor antibodies [IFAs]), and early-stage AIG. These criteria defined "confirmed AIG" as cases testing positive for autoantibodies and having positive endoscopic and/or histological findings, whereas "suspected AIG" was defined as cases negative for autoantibodies but with suggestive endoscopic and/or histological findings.[37]

Endoscopically, AIG is characterized by prominent submucosal vasculature in the gastric fundus and body (Fig. 2A) and severe, corpus-dominant atrophic gastritis, characterized by the absence of folds along the greater curvature. As the disease progresses, the residual oxyntic gland mucosa may appear as pseudopolyps, island-shaped structures, or flat and extensive lesions. The pyloric antrum is generally less severely affected (Fig. 2B); however, approximately 30% of cases show diverse mucosal patterns, such as patchy redness or circular, wrinkle-like patterns.[38,39] Using image-enhanced endoscopy, the mucosa of the gastric body often exhibits a polygonal vascular network, giving it a cast-off skin appearance. Approximately 30% of patients show a white globe appearance, which may also be associated with the use of acid-suppressing agents.[38-40] How-

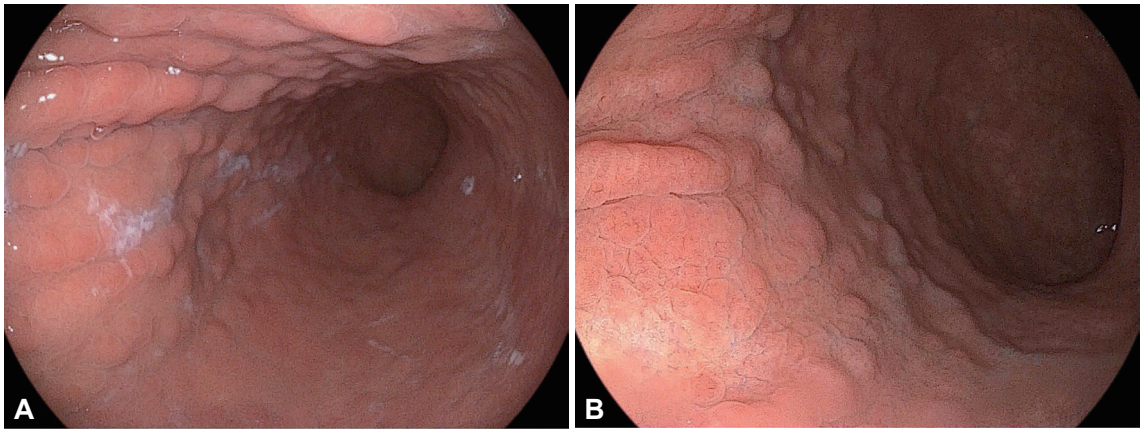

Fig. 3. Endoscopic findings in the early stage of autoimmune gastritis. A: A bamboo joint-like appearance is observed in the greater curvature of the gastric body. B: Pseudopolyps are observed in the greater curvature of the gastric body.

ever, AIG can be easily overlooked during endoscopy, particularly in patients with comorbid *H. pylori* infections and atrophy of the pyloric antrum, which reduces diagnostic accuracy.[41] In early AIG, i.e., in non-atrophic or early-stage AIG, endoscopic findings may not be prominent. To date, case studies have identified a bamboo joint-like appearance (Fig. 3), characterized by vertically aligned pseudopolyps in the gastric body, and a salmon roe-like appearance, marked by edema with erythema of the gastric mucosa, as characteristic endoscopic findings of early AIG before it has progressed to complete endoscopic atrophy.[42] Additional clues include irregular collecting venules, a yellowish-white cobblestone-like appearance, and a mosaic pattern with mild mucosal swelling.[43] These subtle findings imply that careful observation is required to identify early AIG cases.

The diagnostic standard for atrophic gastritis, including AIG, involves performing biopsies. The updated Sydney system is the recommended standard for atrophic gastritis biopsies; this system advises tissue sampling from the greater and lesser curvatures of the gastric body, the pyloric antrum, and the angularis.[44] Pathologically, AIG can be divided into three stages based on the progression of corpus atrophy: 1) early stage, characterized by a mild decrease in parietal and chief cells, less than moderate lymphocyte infiltration, and pseudopyloric metaplasia; 2) florid stage, marked by significant damage to the gastric glands, a foveolar epithelium-to-oxyntic gland ratio of less than 1, the presence of pancreatic or IM, and ECL cell hyperplasia identified using chromogranin A immunohistochemical staining (Fig. 2C-F); and 3) end stage, defined by the near-complete loss of gastric glands and moderate to severe IM.[37] To evaluate the cancer risk in patients with chronic atrophic gastritis, the operative link for gastritis assessment (OLGA) and operative link on gastritis for IM (OLGIM) are used as the pathological assessment systems. In patients with AIG, advanced pathological stages correlate with higher OLGA scores.[45] However, their OLGA and OLGIM scores may remain low because of minimal atrophy in the pyloric antrum and because pseudopyloric metaplasia is excluded from OLGIM scoring, which reduces the reliability of statistical interpretations.[46] In patients with *H. pylori*-induced gastritis, atrophy usually begins in the pyloric antrum and progresses to the gastric body; however, antral atrophy may gradually recover after eradication therapy.[47] Such recovery can make it challenging to differentiate between corpus-dominant atrophic gastritis associated with post-*H. pylori* infection and AIG, potentially causing misdiagnoses or classification errors. Therefore, endoscopic findings of corpus-restricted atrophy and *H. pylori*-negativity are insufficient for an accurate diagnosis of AIG.[48]

THE ROLE OF AUTOANTIBODIES IN DIAGNOSING AIG: ANTI-PARIETAL CELL AND INTRINSIC FACTOR ANTIBODIES

Parietal cells play a critical role in maintaining gastric acidity by producing gastric acid and in facilitating the absorption of vitamin B12 (cobalamin) through intrinsic factor expression.[49] The autoimmune response mediated by $CD4^+$ Th1 cells leads to the activation of B cells and plasma cells, which result in the production of immunoglobulins (IgG, IgA, and IgM). In the serum, this includes IgG, IgA, and IgM classes of PCAs and IgG IFAs; in gastric juice, IgG and IgA PCAs and IgA IFAs are observed.[50] The H^+/K^+ ATPase proton pump, a multipass transmembrane protein, in parietal cells consists of two catalytic α subunits and two β subunits that anchor it to the cell membrane. Although PCAs recognize both subunits as antigens, the α subunit is the primary antigen. Type I IFAs (blocking antibodies) account for approximately 70% of IFAs and

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function by preventing intrinsic factor binding to vitamin B12. Type II IFAs (binding antibodies) represent 30%–40% of IFAs and function to inhibit the absorption of the intrinsic factor–vitamin B12 complex into the small intestine.[50,51]

These autoantibodies, although useful in screening for suspected AIG, have limited diagnostic utility. PCAs may appear positive in 2.5%–9% of healthy adults and in individuals with other autoimmune diseases, such as autoimmune thyroid disease and type 1 diabetes.[52] Similarly, IFAs, which are known markers of pernicious anemia, can test positive even in patients without megaloblastic anemia or vitamin B12 deficiency.[53] Additionally, patients with AIG may test negative for autoantibodies. A recent case study from Japan described patients with ultra-early AIG who tested negative for autoantibodies, presumably as insufficient time had passed for the immune response to produce detectable antibodies.[54] Another study found that approximately 20% of patients diagnosed with AIG are seronegative; these patients are significantly older (average age ≥65 years) than seropositive individuals.[55] This observation suggests that widespread oxyntic gland damage leads to parietal cell depletion and, over time, to immunosenescence.[56,57] However, if antibody titers decrease over time, patients diagnosed with AIG but who are PCA-negative would be expected to exhibit more severe histological damage. Nevertheless, no significant histological differences were observed between these and PCA-positive patients.[55] The study employed a cross-sectional design; therefore, the dynamics of antibody titer changes over time remain unknown, underscoring the need for prospective longitudinal studies to better understand autoantibody conversion and its clinical implications.

Indirect immunofluorescence is commonly used for the detection of autoantibodies in clinical practice. More sensitive quantitative methods include solid-phase immunoassays, such as enzyme-linked immunosorbent assays (ELISAs), and solution-phase immunoassays, such as luminescent immunoprecipitation systems and fluorescent enzyme immunoassays. However, challenges, such as interpretation time, operator skill, and interobserver variability, limit the standardization of autoantibody detection. Future research should focus on developing reliable diagnostic and follow-up testing methods for patients with AIG.[58]

THE ROLE OF SERUM PEPSINOGEN AND GASTRIN IN DIGANOSING AIG

Apart from PCA, other serologic markers have been proposed for the diagnosis of AIG. Serum pepsinogen (PG) and gastrin levels are highly useful for evaluating corpus-dominant atrophic gastritis.[59] PG I, secreted by the chief cells and mucus neck cells of the oxyntic glands, is reduced in patients with AIG, whereas PG II, produced throughout the stomach and the proximal duodenum, is decreased in those with antral atrophy.[3,12] A reduction in the PG I/II ratio indicates not only corpus-dominant atrophic gastritis but also *H. pylori* infection in patients.[60] Notably, several studies have shown that PG I levels and the PG I/II ratio are significantly lower in patients with AIG than in those with *H. pylori*-induced atrophic gastritis. One study reported PG I levels of 24.5 μg/L in patients with AIG versus 80.0 μg/L in patients with *H. pylori*-induced atrophic gastritis (p=0.001) using a chemiluminescent enzyme immunoassay (CLEIA).[61] Other studies found that PG I levels and PG I/II ratios were lower (p<0.001) using ELISA and CLEIA[62]; PG I and PG II levels and the PG I/II ratio were lower (p<0.05) using ELISA in patients with AIG compared with those with *H. pylori*-induced atrophic gastritis.[63] These findings suggest that atrophy is more severe in patients with AIG than in those with *H. pylori*-induced atrophic gastritis and indicate that PG levels may serve as markers for differentiating the causes of advanced atrophic gastritis. Since the PG I/II ratio is influenced by changes in both PG I and PG II, its interpretation can be challenging. However, in patients with corpus-dominant atrophic gastritis (a characteristic finding of AIG), the decrease in the PG I/II ratio is closely associated with a reduction in PG I levels.[64] Therefore, the combined use of PG I levels and the PG I/II ratio may serve as a valuable diagnostic marker for AIG. Clinical studies conducted over the past five years have used cutoff value ranges for PG I levels (9.8–38.7 μg/L) and the PG I/II ratio (0.8–3.1) to indicate AIG (Table 1).[62,63,65-67]

In patients with AIG, where parietal cells are damaged and acid secretion is impaired, gastrin levels may be abnormally elevated. Gastrin has been identified as a marker of progression from potential AIG to overt AIG, reflecting the extent of mucosal damage.[28] Elevated gastrin levels also play a critical role in inducing abnormal ECL cell proliferation, which is a key factor in the development of gNEN.[68] A PG I/II ratio below 2.3 and a serum gastrin level exceeding 29.6 pmol/L (61.5 pg/mL, 95% distribution reference value range: 2.5–7.0 pmol/L) are associated with an increased risk of gNEN in patients with AIG.[69] However, the accuracy of non-invasive markers for early gNEN diagnosis is relatively low, with a sensitivity of approximately 50% and a specificity of approximately 60%.[70] Additionally, elevated serum gastrin levels can be influenced by *H. pylori* infection or by acid-suppressing agents, necessitating the confirmation of *H. pylori* status and discontinuation of acid-suppressing medications for more than 14 days before testing.[12,71]

In patients with AIG, PG and gastrin levels can be considered useful biological markers that not only predict histologi-

Table 1. Diagnostic cutoff values for PG I, PG I/II ratio, and gastrin in AIG patients reported in studies

Study	Year	Criteria for diagnosis of AIG	Number of patients	Age of patients (yr)	PCAs	*H. pylori* infection	PG I (μg/L)	PG I/II ratio	Gastrin (reference range)	Serological testing method
Ogutmen Koc and Bektas[63]	2022	Histology	16	57.7±12	12 (75)	6 (37.5)	13.5	1.9	NA	ELISA
Kishikawa et al.[65]	2022	Serology, histology	31	73 (66–76)*	29 (93.5)†	14 (45.2)	9.8	1.8	355 pg/mL (<140 pg/mL)	CLEIA (PG), RIA (gastrin)
Wada et al.[66]	2022	Serology, histology	22	65.2±10.8	22 (100)	12 (54.5)	14.5	2.1	172 pg/mL‡	CLEIA
Chapelle et al.[62]	2023	Histology	44	58.8±14.2§	NA	7 (14.9)	38.7	3.1	NA	ELISA
				58.6±14.2§			16.3	2.33	NA	CLEIA
Guo et al.[67]	2023	Serology, histology	46	64 (55–71)‖	46 (100)	18 (39.1)	14.2	0.8	107.5 pmol/L (1–75 pmol/L)	ELISA

Data are presented as mean±standard deviation, median (interquartile range), or n (%).
*Cases of atrophic gastritis, including environmental atrophic gastritis and autoimmune atrophic gastritis; †Anti-parietal cell antibody positive (n=29/31), intrinsic factor antibody positive (n=15/27); ‡Normal cutoff value for screening autoimmune gastritis; §Cases of chronic atrophic gastritis, including non-autoimmune atrophic gastritis and autoimmune gastritis; ‖Cases of gastric premalignant lesions, including gastric atrophy and gastric intestinal metaplasia.
AIG, autoimmune gastritis; PG, pepsinogen; PCAs, anti-parietal cell antibodies; NA, not available; ELISA, enzyme-linked immunosorbent assays; CLEIA, chemiluminescent enzyme immunoassay; RIA, radioimmunoassay.

cal progression and complications, but that also assist in diagnosis through pre-endoscopic screening.[15,72] However, the Japanese diagnostic criteria did not adopt these as diagnostic markers due to their lack of specificity.[37] Along with prospective studies on surveillance using these serologic markers, further research that minimizes sampling errors and includes a large patient population is needed to determine whether they can be utilized in the diagnostic criteria for AIG.

GASTRIC NEOPLASMS DEVELOPMENT IN AIG

The pathophysiology of gastric neoplasms in patients with AIG encompasses a wide range of factors, including genetics, epigenetics, lymphocytes, cytokines, oxidative stress, infections, protein expression, and microRNAs.[73] In these patients, the neoplastic lesions can vary widely and may include hyperplastic polyps, fundic gland polyps, gNENs, intraepithelial dysplasia, and gastric cancer. Positive PCAs, a low PG I/II ratio, and ECL cell hyperplasia are factors predicting the development of neoplastic lesions.[74] A cross-sectional study of patients with AIG over a 4-year period revealed that 36% developed neoplastic lesions, with gNENs identified in more than 40% of these cases.[46] The incidence of gNENs has increased more than 15-fold with the growing use of endoscopy and heightened interest in the disease.[75] Type 1 gNENs, which account for over 70% of cases, is characterized by hypergastrinemia and hypo- or achlorhydria. AIG is one of the key causes of gastrin-dependent gNENs, as corpus-dominant atrophic gastritis and hypergastrinemia induce the hyperplasia of ECL cells.[5] The annual incidence rate of type 1 gNENs in patients with corpus-dominant atrophic gastritis was 2.8% over a median follow-up of 5 years, and it was more than twice as high in patients with pernicious anemia, which is a late clinical manifestation of AIG.[76] However, the exact mechanisms underlying type 1 gNENs have not been fully elucidated yet, and further studies are needed to investigate the gastric microenvironment and its effects, along with the trophic action of gastrin.

The relationship between AIG and gastric cancer remains a topic of debate. A meta-analysis has reported that patients with AIG face an up to an 11-fold increased relative risk of gastric cancer, with the annual incidence of low-grade intraepithelial neoplasia, a precancerous condition, being more than three times that of gastric cancer.[77] However, early studies on pernicious anemia and recent research on precancerous lesions have often been limited by inconsistent diagnostic criteria, small sample sizes, short follow-up periods, and population heterogeneity due to the inclusion of diverse ethnic groups within Western cohorts.[77,78] Gastric cancer in patients with AIG

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is often characterized by its presence in older individuals, localization in the upper body or greater curvature of the stomach, and higher rates of synchronous and metachronous tumors.[79] Patients with AIG who undergo endoscopic resection for gastric cancer show a more than three-fold higher rate of metachronous tumors.[10] In Asia, including South Korea, the reported incidence of early gastric cancer in patients with AIG and autoantibody-positivity ranged from 1.3% over 2.5 years to 5.9% over 3 years.[11,79,80] However, these findings were based on retrospective studies that often involved small sample sizes, lacked standard biopsy protocols, included limited data on IFAs, included patients with false-positive autoantibody detection, or excluded autoantibody-negative cases.

In a recent prospective follow-up study, *H. pylori*-negative patients with AIG were not found to develop gastric cancer.[81] However, this finding may have been affected by factors such as the younger average age of the participants, lack of serum markers indicating the extent of atrophy, and possible exclusion of autoantibody-negative patients with AIG.[82,83] Some studies and experts have suggested that the lower incidence of gastric cancer among patients with AIG, compared with those with *H. pylori*-induced gastritis, may be due to lower mucosal cell proliferation, reduced infiltration of macrophages involved in this process, and the rarity of incomplete-type IM, which carries a high risk for gastric cancer development.[84-87]

Although *H. pylori* infection has been considered a cause of gastric cancer, some patients with AIG have developed gastric cancer without evidence of *H. pylori* infection, leading to the absence of a statistically significant association between *H. pylori* infection and the neoplastic process.[74,88] Research in mice and human tissues has shown no histopathological differences between *H. pylori*- and AIG-induced metaplasia and no differences in transcriptional processes or subtypes of metaplastic cells associated with gastric cancer, indicating that AIG poses an independent risk for gastric cancer.[89] Studies in patients with AIG have reported gastric cancer-related findings, including reduced tricarboxylic acid cycle proteins, increased intercellular adhesion proteins (e.g., cadherins), abnormal DNA methylation in gastric tissues, and elevated microRNA-21 levels in the plasma.[90-92] Parietal cell damage in patients with AIG alters the gastric acid environment, leading to reduced vitamin C activity and bacterial overgrowth that produces nitrites. This results in decreased nitric oxide synthesis and an increase in carcinogenic nitrosamines.[93] The altered gastric environment also contributes to dysbiosis.[94] In *H. pylori*-negative patients with AIG, bacteria of the phylum Firmicutes, such as the oral commensal *Streptococcus*, are predominantly present. Furthermore, in patients with AIG accompanied by gastric cancer, elevated levels of *Bacillus cereus* have been observed.[95-97]

Table 2. Characteristics of studies on neoplastic lesions

Study	Year	Sources of selection	Study design	Criteria for diagnosis of AIG	Number of patients	Duration of follow-up (yr)	Age at diagnosis (yr)	Female (%)	PCAs (%)	*H. pylori*, % (status of infection)	Cases of gastric neoplasm		
											LG IED	GC/HG IED	gNEN
Massironi et al.[46]	2025	Multi-center	Cross-sectional	Histology	612	7	59 (48–68)	73.9	81	21.2 (past, current)	26 (4.2)	12 (2)	108 (17.6)
Lenti et al.[36]	2024	Multi-center	Retrospective	Histology	1598	7.4 (89 months)	58 (46–68)	73.3	83.2*	27.5† (past)	NA	15 (0.9)	153 (9.6)
Miceli et al.[28]	2024	Single-center	Prospective	Histology	498	4.3 (52 months)	56.7±15.2	71.5‡	77.7	4.8 (past)	14 (2.9)	4 (0.8)§	23 (4.8)
Dilaghi et al.[76]	2023	Single-center	Prospective	Histology	275	5	61 (23–84)	71.6	84.1	36.7 (past, current)	9 (3.3)	7 (2.5)	28 (15.3)
Massironi et al.[88]	2023	Single-center	Retrospective	Histology	176	5	64 (53–71)	80.7	85.7	20.4 (past, current)	6 (3.4)	1 (0.6)	33 (18.8)
Rugge et al.[81]	2023	Single-center	Prospective	Serology, histology	211	7.5	55.7±14.1	75.8	100‖	0 (naïve)	5 (2.4)	0	11 (5.2)

Data are presented as mean±standard deviation, median (interquartile range), or n (%) unless otherwise indicated.
*PCAs negative (n=242), PCAs positive (n=1198); †*H. pylori*-naïve (n=1079), *H. pylori*-positive (n=411); ‡Female:male=2.5:1; §High grade dysplasia (newly onset neoplastic complications in 41/483 patients); ‖PCAs and/or intrinsic factor antibodies.
AIG, autoimmune gastritis; PCAs, anti-parietal cell antibodies; LG IED, low grade intraepithelial dysplasia; GC, gastric cancer; HG IED, high grade intraepithelial dysplasia; gNEN, gastric neuroendocrine neoplasm; NA, not available.

These may potentially provide insights into the mechanisms underlying gastric cancer development. Table 2 summarizes the incidence of neoplastic lesions, including gastric cancer, in patients with AIG, based on recent single- and multicenter studies reported after the latest meta-analysis conducted in 2023.[77]

The optimal interval for endoscopic and histologic surveillance in patients with AIG remains a subject of ongoing discussion. Given the negligible risk of gastric malignancies in patients with *H. pylori*-negative primary AIG, a 3–5-year interval for endoscopic surveillance is recommended.[2,15] Biopsy follow-ups should be considered based on endoscopic findings and clinical indications, with a primary focus on the early detection of gNENs rather than the secondary prevention of gastric cancer.[15] Future research should aim to develop appropriate follow-up strategies, consideration of the pathophysiological features of the disease, changes in the gastric environment, and the risks of neoplastic lesions and synchronous/metachronous tumors.

CONCLUSION

AIG remains underdiagnosed and requires proactive efforts to improve its diagnosis and management. Although clinical practice guidelines for gastritis in South Korea exist, they do not include information on AIG; established guidelines for its diagnosis are also currently unavailable.[98] AIG should be considered in patients with reverse atrophy, autoimmune disease, or unexplained micronutrient deficiency. AIG diagnoses may be delayed in patients with vague neurological symptoms or persistent gastrointestinal complaints[99]; in such cases, a high index of suspicion and a more vigilant diagnostic approach are warranted. Serological tests for PG and gastrin and endoscopic evaluations specifically targeting AIG should be performed. If corpus-dominant atrophic gastritis or abnormal serological results are detected, autoantibody testing (PCAs, IFAs) is warranted, and standard biopsies are required for confirmation (Fig. 4). After an AIG diagnosis, serological tests can assess micronutrient deficiencies (e.g., microcytic or macrocytic anemia) and coexisting autoimmune diseases, particularly autoimmune thyroiditis, by measuring mean corpuscular volume, hemoglobin, ferritin, vitamin B12, and thyroid-related markers, including thyroid function, thyroid peroxidase antibody, and anti-thyroglobulin antibody levels.[100]

Currently, no curative treatment is available for AIG. However, individualized, patient-centered management is essential, focusing on controlling symptoms, improving quality of life, correcting micronutrient deficiencies, and surveilling for neoplastic risks, including gastric cancer.

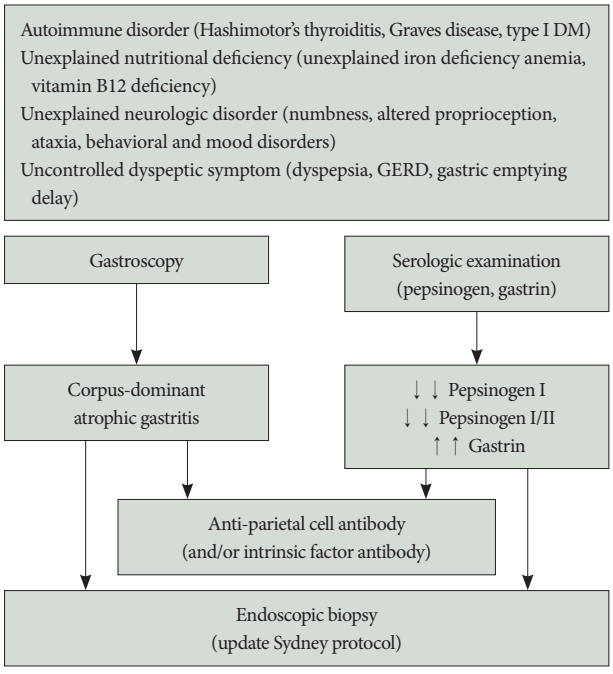

Fig. 4. Flowchart for the diagnosis of autoimmune gastritis. DM, diabetes mellitus; GERD, gastroesophageal reflux disease.

Authors' Contribution

Conceptualization: Yong Hwan Ahn. Writing—original draft: Yong Hwan Ahn. Writing—review & editing: Yong Sung Kim. Approval of final manuscript: all authors.

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