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Monitoring the follow-up of autoimmune chronic atrophic gastritis using parietal cell antibodies and markers of gastric function

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ABSTRACT

Increased interest in the pathogenesis and the evolution of autoimmune chronic atrophic gastritis (A-CAG) has led to the search for serological markers that can be used to detect changes in the gastric mucosa at an early stage and to monitor the course of the disease. Parietal cell autoantibodies have been proposed as suitable immunological markers of atrophic damage, as they can be detected in the serum when symptoms of gastritis are not yet present. However, the utility of measuring only the level of parietal cell autoantibodies in the follow-up of A-CAG does not appear to suffice. Recent evidence has suggested that, in monitoring A-CAG, parietal cell antibodies should be associated with an evaluation of gastric function through biochemical and hormonal tests, such as pepsinogens and gastrin 17. This integrated approach will allow for the more effective real-time monitoring of the state of the gastric mucosa. As A-CAG is a progressive disorder associated with an increased risk of gastric cancer and neuroendocrine tumors, the precise follow-up of patients with gastric atrophy needs to be better defined. Further longitudinal studies in large cohorts must be performed with long-term follow-up.

1. Introduction

Chronic gastritis represents a condition characterized by a degenerative process that frequently evolves into atrophy due to the loss of cellular components of the gastric mucosa [1–5]. As it was difficult to diagnose until a few decades ago, chronic atrophic gastritis (CAG) has drawn the attention of the scientific community because of its characteristic of being a precancerous condition that can lead to the development of both gastric adenocarcinoma and gastric type 1 neuroendocrine tumors [6,7]. Compared with other gastrointestinal disorders, CAG is considered relatively rare. However, serological studies conducted in different parts of the world have reported a CAG prevalence of up to 27 % in the general population [7–9]; these percentages, however, may vary greatly depending on the diagnostic criteria used (serological, clinical, or endoscopic/histological). Data on its incidence are scarce and not homogeneous due to the different clinical settings in which the diagnoses are made and few longitudinal studies were performed to date. In the meta-analysis conducted by Adamu et al. from 14 selected follow-up studies in symptomatic or high risk populations who were diagnosed to be free of CAG at baseline, the incidence varied from 0.2 % to 10.9 % [10].

Depending on the etiological causes responsible for the damage, the anatomical location, and the extent of the atrophy, CAG can be separated in two distinct clinical forms: CAG associated with Hp infection (Hp-CAG), which starts from the antrum and eventually diffuses into multifocal gastritis, and CAG associated with autoimmune processes (A-CAG), which is limited to the gastric body mucosa. Mixed forms of Hp-CAG and A-CAG are also known [11].

Over the past few decades, most studies have focused on Hp-CAG, considering the important effects of the infection on the evolution of gastric cancer. However, the beneficial effects on the gastric mucosa obtained after the introduction of eradication therapy have not led to a reduction in the prevalence of CAG, highlighting that the second form of CAG, the autoimmune one, is an underestimated disease, especially in populations characterized by a high prevalence of gastric cancer (Asiatic areas) [12,13]. The observation that, despite the declining prevalence of chronic Hp infection, the presence of gastric alterations may remain, indicates that A-CAG is a major risk factor for gastric atrophy [14].

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2. A-CAG: epidemiology and clinical aspects

A-CAG is an organ-specific, immune-mediated inflammatory disorder characterized by the destruction of the gastric oxyntic mucosa, leading to the loss of parietal cells, with these being replaced by atrophic and metaplastic tissue. It shows a predilection for the female gender (M/F ratio 1:2–3) [15,16] and for subjects older than 60 years, although a Swedish study reported the highest prevalence between 35 and 45 years [17].

Considering the general population, the prevalence of A-CAG is estimated to range from 0.1 % to 1–2%; however, a higher prevalence (0.5–4.5 %) has been detected in northwestern populations [18–20], which may increase up to 7.8–19.5 % in selected cohorts, such as those including subjects with iron-deficient anemia refractory to iron supplementation [21–26].

From a clinical point of view, hematological alterations represent the main clinical presentation, as a result of micronutrient deficiencies; however, as micronutrient deficiencies take time to develop, A-CAG may remain clinically silent for many years [7,27–33]. Within the hematological findings, a common presentation is microcytic iron deficient anemia that could be present as a consequence of iron malabsorption for a reduced conversion of Fe^{3+} to Fe^{2+} due to decreased acid secretion into the stomach. Macrocytic (also called pernicious) anemia generally represents a late-stage manifestation of A-CAG characterized by megaloblastic anemia due to vitamin B12 malabsorption induced by intrinsic factor (IF) deficiency [16]. IF is responsible for binding vitamin B12 and facilitating uptake in the terminal ileum; when parietal cell loss occurs, the reduced bioavailability of this molecule is due to reduced production as well as autoantibodies targeting IF. The presence of an iron deficient anemia can be seen in the early stage of A-CAG, especially in younger women, showing that iron stores are depleted more quickly than vitamin B12 stores. Pernicious anemia usually represents a late-stage manifestation of A-CAG and is more common in males and older patients [16].

Another relevant clinical feature is that patients affected by A-CAG are more prone to develop other organ-specific autoimmune disorders to constitute the autoimmune polyendocrine syndromes (APS). Among the various forms of APS, the coexistence in the same patient of autoimmune thyroiditis [34–37] and at least one of the following autoimmune diseases: type 1 diabetes mellitus (T1DM) [38,39], myasthenia gravis [40], vitiligo [41], psoriasis, celiac disease [42,43], atrophic gastritis or pernicious anemia characterizes APS type 3. The APS subtype 3b describes the association among autoimmune thyroid disease, A-CAG and pernicious anemia [44]. Approximately 10–40 % of patients with Hashimoto's thyroiditis, the most common autoimmune disease, present with associated gastric disorders and show a prevalence of A-CAG that is 3–5 times higher than that found in the general population. Conversely, autoimmune thyroiditis is present in almost 40 % of patients with established A-CAG. This correlation could be explained by considering that the thyroid gland and the stomach share similar immunologic properties, most likely due to their common embryologic origin [45].

3. Pathogenic mechanisms of A-CAG

A-CAG is an immuno-mediated chronic inflammatory disease that affects the corpus fundus mucosa of the stomach [46,47]. The process of cellular degeneration results from the interaction of $CD4^{+}CD25^{-}$ T lymphocytes, B lymphocytes, and macrophages (originating from multifocal lymphocytic and plasma cell infiltration of the oxyntic mucosa) with proteins secreted by gastric parietal cells or located on their surface. In particular, T helper 1 (Th1) cells produce a series of pro-inflammatory cytokines, such as interferon-gamma, while T helper 17 (Th17) cells secrete interleukin (IL)-17 and IL-21 which, together with other pro-inflammatory molecules, contribute to progressive destruction of the gastric glands [48]. Autoreactive Th1 cells can promote gastric epithelial cell death by activating the Fas–Fas ligand and perforin/granzyme B cytotoxic pathways and amplifying the expression of Fas and major histocompatibility complex class II molecules on the gastric epithelial cells, inducing them to function as antigen-presenting cells [49].

The dysregulation of the immune system leads to the loss of tolerance towards self-antigens localized on the gastric mucosal cells and to the consequent appearance of circulating antibodies produced by plasma cells and directed against the enzyme H^{+}/K^{+}-ATPase present on the surface of gastric parietal cells (IgG parietal cell autoantibodies, PCAs) and their product, the intrinsic factor (IgG anti-intrinsic factor autoantibodies, IFAs) [50–55]. The activation of cell-mediated and humoral immunity, in turn, stimulates the secretion of other Th1 cytokines in a self-maintaining loop: $CD4^{+}$ $CD25^{-}$ T lymphocytes fuel and potentiate the inflammatory reaction with the recall of macrophages and B lymphocytes that infiltrate the submucosa, the lamina propria, and the gastric glands, causing atrophy [52]. The chronic T cell dependent B cell activation is responsible for the local production of H+/K + ATP-ase autoantibodies which are usually detected in the serum of A-CAG patients [49]. Therefore, PCAs may not be directly involved in the pathogenesis of A-CAG, but might be the consequence of damage to the parietal cell H+/K + -ATPase induced by autoreactive T cells [47].

4. Immunological markers of A-CAG

Traditionally, the diagnosis of A-CAG relies on clinical and laboratory findings, necessitating confirmation through the identification of characteristic histopathological alterations [7,13]. Increased interest in the pathogenesis and evolution of A-CAG has led, over the past two decades, to the search for serological markers that are able to detect the possible changes in the gastric mucosa at an early stage [56].

4.1. PCAs

The correlation between PCAs and A-CAG has been known since the 1960s, when they were discovered and the first analytical methods for their measurement were developed [13]. The appearance of these antibodies in the serum of patients represents the first signal to suspect a gastric anomaly (atrophy, vitamin B12 deficiency, pernicious and/or microcytic anemia) [57,58]. Therefore, PCAs should be considered a serological hallmark of A-CAG, and their early detection in the serum is of clinical significance, especially in those patients in which the symptoms of gastritis are not yet present.

In the general population, the prevalence of PCAs increases with age, from 2.5 % in the third decade to 12 % in the eighth decade [59], while they are present in 80–90 % of patients with A-CAG [53,60]. Quantitative variations in PCAs titers can be observed, depending on the extent of gastric atrophy; they tend to gradually decline from early-to late-stage A-CAG and may eventually disappear in late-stage patients. Indeed, Conti observed an inverse correlation between the patients' age and the PCAs titer [61]. This observation might be explained by considering that autoantibody levels increase progressively over time, reach a peak level, and then fall, as a result of the ongoing destruction of the gastric mucosa and the disappearance of the target autoantigen H+/K + -ATPase [46]. Hence, the absence of PCAs does not exclude the possibility of late-stage atrophic damage.

In addition to A-CAG, PCAs may also be found in other conditions, including several autoimmune diseases [62]. They may be detected in 20–30 % of subjects with autoimmune thyroid diseases, often at high level [34,55]. PCAs are also more prevalent in T1DM patients with a higher rate in adults (13–20 %) than in children (5 %), in individuals with vitiligo (15 %), in celiac disease patients (3–10 times more often) and in their first- and second-degree relatives [55]. It has been demonstrated that the presence of PCAs in these individuals puts them at a higher risk of developing A-CAG. It follows that in patients affected by these diseases, the possible presence of PCAs needs to be sought in order to investigate an occult (asymptomatic) or initial A-CAG condition. If PCAs are found, a histological examination should be assessed based on

Table 1
Histological changes, prognosis and follow up of patients affected by autoimmune chronic atrophic gastritis (A-CAG) (ECL: endocrine cell like; gNET: gastric neuroendocrine tumor; PGI: pepsinogen I; PGII: pepsinogen II; G17: gastrin-17; PCAs: parietal cell antibodies).

Features [and ref.]	What is known	Translational impact
Immune infiltrate [85]	Corpus restricted monocuclear inflammation characterized by prominent lympocytic infiltrate and few macrophages	The lack of macrophages may lead to a more benign pattern of metaplasia and abrogate against the increased risk for adenocarcinoma
Histopathological progression [73,81,84,85]	Atrophic gastritis - Pyloric metaplasia - Complete intestinal metaplasia or Atrophic gastritis - ECL cell hyperplasia – gNET	A-CAG is a steadily progressive disease with no cases of atrophy regression. gNET is a rather frequent finding, therefore an early diagnosis is important to improve the prognosis
Natural history [73]	The long term natural history of both overt and potential A-CAG and the risk of developing neoplastic complications are only partially known	A substantial proportion of patients with potential A-CAG will develop overt A-CAG at follow up
Prognosis [6,73,84,85]	Good No association between A-CAG and gastric cancer (except for past/actual coexisting Hp infection)	In patients with gNET and dysplasia the risk of developing overt gastric neoplasia is virtually absent or very rare; however, follow up of A-CAG patients remains important to identify the possible progression of lesions towards carcinoid neoplasia taking into account other potential risk factors for gastric cancer
Follow up [81,84]	Patients with both A-CAG and gNET have a lower PGI/PGII ratio and higher G17 levels than A-CAG without such tumors	Determination of PGI, PGII and G17 may help to identify those at risk of gNET. If PCAs is important in diagnosing A-CAG patients, its role in monitoring the atrophic gastritis evolution is less significative

the results of gastric function tests.

Finally, PCAs can be found, with a significance that is still unclear, in 2.5–9% of healthy adults [55]. This prevalence, derived based on screening procedures carried out on healthy individuals, varies depending on the assay used; however, it is unknown why a fraction of these seropositive people, who present no signs or symptoms, never develop A-CAG [63]. Regarding the meaning attributed to PCAs in subjects without an atrophic stomach, it is possible to hypothesize that their presence indicates a very early phase of gastric autoimmunity, which could evolve to atrophy over time or remain stable, without functional consequences. It should be considered that, similar to many other autoimmune diseases, PCAs may be present in the preclinical or subclinical phase of A-CAG when the functions of the target organ are conserved or offset by homeostatic mechanisms [16,64].

4.2. IFAs

Other autoantibodies that are detectable in the serum of patients affected by A-CAG are those directed against the IF. The IF is secreted by gastric parietal cells; under normal conditions, it binds through a high-affinity bond to vitamin B12, facilitating its transport to the terminal ileum, where it is absorbed. During A-CAG, the sequestration of the molecule by the related autoantibodies reduces intrinsic factor bioavailability, resulting in a lower or failed vitamin B12 absorption, with the consequent onset of pernicious anemia [53]. IFAs are present in approximately 80 % of patients with pernicious anemia; they are more specific than PCAs (98.6 % vs. 90 %) for A-CAG, but the sensitivity is lower (37 % vs. 81 %), increasing during disease progression [65].

5. Role of PCAs and IFAs in diagnosing A-CAG

The *Management of Epithelial Precancerous Conditions and Lesions of the Stomach (MAPS 2019)* guidelines [66] indicate that, in addition to intestinal metaplasia and gastric body atrophy, patients with A-CAG warrant surveillance for the early detection of gastric cancer. In the early stages, this surveillance can be challenging owing to the lack of specific symptoms and the fact that this disease may be underestimated. PCAs and IFAs have been proposed as suitable immunological markers of atrophic damage as a noninvasive, pre-endoscopic assessment of A-CAG [53,67].

As mentioned above, PCAs are positive in 85–90 % of A-CAG patients. Slight variations may be due to the methods used for their detection [68]. The specificity is suboptimal, being influenced by the stage of disease and by the presence of other autoimmune diseases. Despite being less sensitive, IFAs are more specific than PCAs [53,69]. The real diagnostic utility of this marker has not yet been clearly defined because conflicting studies exist. In Lahner's study, IFAs, when considered alone, showed 37 % sensitivity but, when combined with PCAs, the sensitivity increased up to 73 % in patients with pernicious anemia [53]; this evidence, however, was not confirmed in another study that found limited value for IFAs in patients who were negative for PCAs identified through immunofluorescence [70].

In general, PCAs are detectable in the initial phases of A-CAG, whereas the detection of IFAs becomes more pertinent during the advanced stages. In the initial stages of A-CAG, we can detect PCAs because the antibodies are directed against a surface antigen and the cells are not yet completely destroyed. IFAs appear later in the clinical course because the intrinsic factor is a molecule produced inside of gastric parietal cells, and therefore, the antigenic stimulus is weaker and occurs later [12,71]. In the very advanced stages of A-CAG, IFAs disappear, together with the disappearance of PCAs due to the significant depletion of parietal cells.

Considering the low prevalence of A-CAG in the general population (0.1–2%), the negative predictive value of PCAs for the presence of A-CAG is very high (99 %). For this reason, PCAs have been proposed for screening purposes in open populations [71].

On the other hand, in high risk groups a positive PCA result could indicate an unrecognized ongoing disease [71]. However, as the sensitivity of this marker is only about 80 %, a diagnosis might be missed in some subjects with a negative test [15,16,47,53] with a consequent delay in follow-up and treatment. In a prospective study, Massironi showed that the diagnosis of A-CAG could be better established through the histological confirmation of atrophy of the gastric body mucosa and/or enterochromaffin-like cell hyperplasia, associated with fasting hypergastrinemia and/or the presence of PCAs or IFAs [11].

Similar to celiac disease, the new concept of "potential" autoimmune gastritis has recently emerged [47,72]. Potential A-CAG was defined as the presence of PCAs in the absence of both gastric histopathological corpus atrophy and concurrent Hp infection. A recent prospective study, including 93 patients, evaluated the natural history of potential A-CAG across a median follow-up period of 52 months. The annual rate of progression from potential to overt A-CAG was found to be 10.9 % (95 % confidence interval: 7.8–15.2) [73]. It was reported that approximately 47 % of subjects with potential A-CAG may develop overt A-CAG over a median time of 2 years [60,73].

In this scenario, serum antibody testing represents a valuable diagnostic tool, especially in cases lacking specific symptoms and with a negative histology. Although PCAs may precede the appearance of atrophic lesions of the stomach for several years, their diagnostic use, if

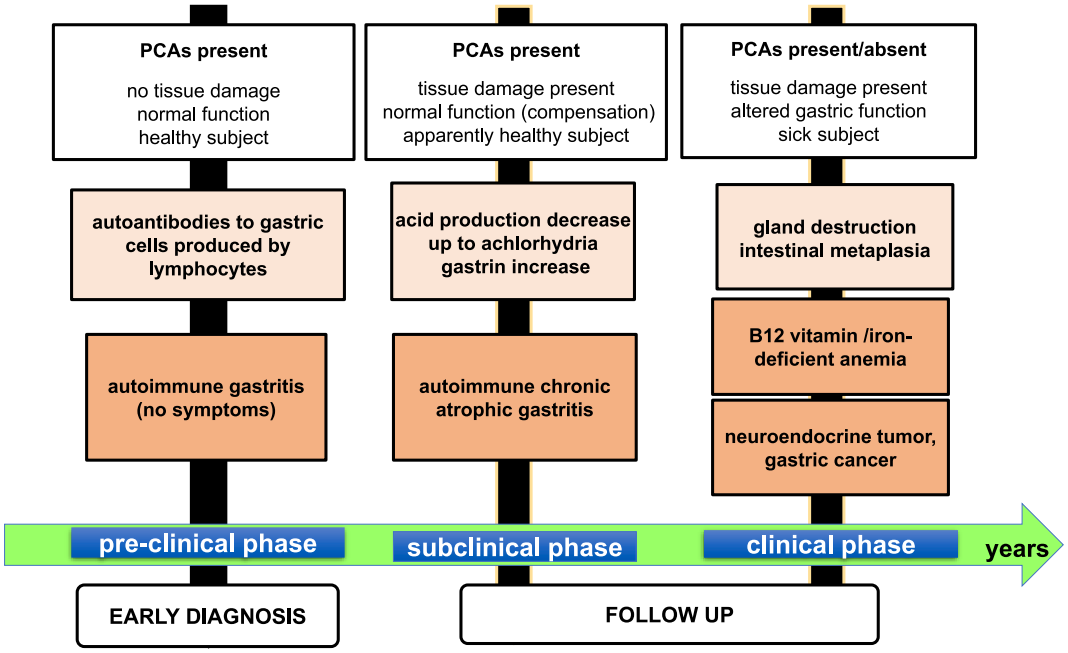

Fig. 1. Schematic representation of events associated to autoimmune chronic atrophic gastritis and role of antibodies to gastric parietal cells (PCAs).

considered alone, is not exhaustive for suspecting an autoimmune atrophic gastric condition [47]. In light of this gap, the combined use of PCAs with biomarkers of gastric function, such as pepsinogens I and II (PGI and PGII), gastrin17 (G17), and anti-Hp antibodies, has been proposed.

The contemporary evaluation of the mechanism of damage and function has already been widely consolidated for other autoimmune diseases. For example, in Hashimoto's thyroiditis, the assay of anti-thyroperoxidase (and anti-thyroglobulin) autoantibodies is never separated from the evaluation of thyroid-stimulating hormone (TSH) as an index of thyroid function. Similarly, in primary biliary cholangitis, the evaluation of antimitochondrial, anti-sp100, and gp210 antibodies is always accompanied by measurements of the levels of transaminases and alkaline phosphatase. We believe the same principle should be applied to gastric autoimmunity.

Under physiological conditions, PGI is secreted only by oxyntic glands of the corpus mucosa and can be detected in serum at a concentration of 70–160 ng/mL. Conversely, PGII is produced both in the corpus and in the gastric antrum and duodenum (normal serum values 3–15 ng/mL). In the presence of gastric atrophy, which is typically restricted to the corpus-fundus, both PGI and PGII levels decrease even if, because of the antral sparing, PGII decline is less than that of PGI. As a result, the ratio of PGI/II is useful in the diagnosis of corpus atrophy. There is a correlation between the decrease in the number of cells in the body-fundus of the gastric mucosa induced by gastric atrophy and the serum level of PGI: PGI values less than 30 ng/mL (and a consequent decrease in the PGI/II ratio below 3), clearly indicate lesions in the body-fundus area [16].

Lowered PGI concentrations will reduce the secretion of hydrochloric acid and induce the compensatory increased production of G17 by the G-cells localized in the antrum. Therefore, low serum PGI levels, a low PGI/PGII ratio and an increased concentration of G17 have been detected in patients with atrophic gastritis [74]. The simultaneous determinations of PGI (or the PGI/II ratio) and G17 together with PCAs constitute the optimal combination for detecting A-CAG, showing good diagnostic accuracy for a noninvasive diagnostic work-up of A-CAG [22,58,69,74,75]. A reduced PGI/II ratio is indicative of functional atrophic impairment, whereas positivity for PCAs suggests the autoimmune nature of the gastric alterations. In a recent work, the PGI/II ratio was found to be the best single biomarker (sensitivity, 79 %; specificity, 90 %; area under the receiver operating characteristic curve (AUC, 0.90), while the combined use of PGI/II and PCAs resulted in an AUC of 0.93 for detecting A-CAG [58]. The authors found that the best combination of biomarkers for detecting A-CAG was PGI/II with PCAs, while the addition of G-17 and IFAs was found of little utility in the diagnosis of A-CAG [58].

6. Role of PCAs in the follow-up of A-CAG

The dynamic change in autoantibody titers has been well-studied for several autoimmune diseases, such as Hashimoto's thyroiditis and celiac disease, in which autoantibodies can reflect the presence and severity of the autoimmune response and variations in their titers may be used as prognostic biomarkers with a role in monitoring disease activity [65,76,77].

Regarding A-CAG, understanding the changes in serum PCAs titers during its progression may be useful for monitoring the course of the disease. However, only a few studies have investigated the dynamic longitudinal changes in PCAs in A-CAG patients, and only a few reports have addressed the question of whether the phases of A-CAG are related to PCA positivity or PCA titers.

Uibo et al. [78] determined the occurrence of PCAs in 199 volunteer subjects (149 from a random sample of an urban population and 50 nonrandom subjects, which were studied side-by-side with those of the other group). They were examined for the occurrence of PCAs and thyroid microsomal antibodies (TMAs) twice in a 6-year interval; the findings compared the state of the gastric antral and fundal mucosa and the fasting level of serum G17. At the beginning of the study, 4/149 and 2/50 subjects were positive for IgG and/or IgA serum PCAs, respectively, while 6/149 and 4/50 were positive for serum IgG and/or IgM TMAs. After 6 years, none of the initially antibody-positive patients in the random group lost their antibodies, while 2/149 new cases of PCAs and 3/149 new TMA cases appeared. Among the nonrandom subjects, only 1/50 new TMA cases appeared at the end of the study. No significant changes in the state of the gastric antral/fundal mucosa in relation to the persistence or appearance of PCAs and/or TMAs were found, as compared with changes in the gastric mucosa in the entire (random and nonrandom) population sample. However, a good correlation was

Table 2
Clinical significance and utility of serological and immunological markers for autoimmune chronic atrophic gastritis (A-CAG) diagnosis and follow up (PGI: pepsinogen I; PGII: pepsinogen II; PGI/PGII: pepsinogen I/pepsinogen II ratio; G17: gastrin-17; PCAs: parietal cells antibodies; IFAs: anti-intrinsic factor antibodies).

Marker	*Trend in A-CAG*	*Clinical significance*	*Diagnosis* [7,17,23,58,74]	*Follow up* [17,46,59,73,75,79,81,84]
PGI	↓↓	A decrease is suggestive for atrophy of the stomach's body. Serum levels decrease in proportion to the severity of atrophy	+++	++
PGII	=	In A-CAG with progressive atrophy level declines less than of PGI due to its production mainly in the stomach's antrum and in duodenum	-	-
PGI/PGII	↓↓	The ratio decreases linearly with the reduction of PGI and with the severity of gastric atrophy	+++	++
G17	↑↑	Increases in response to a reduced acid production and stimulates the proliferation of enterochromaffin-like cells. It's a reliable marker of A-CAG evolution from the potential to an overt disease stage. Higher levels are associated with a more severe disease stage, possibly reflecting the extent of mucosal damage	++	+++
PCAs	↑↑	One of the first signal to suspect A-CAG. Present in 85–90 % of A-CAG patients, but also in 2.5–9% of healthy adults, as well as in people with other autoimmune diseases. Detectable in the initial phases of A-CAG, tend to fluctuate over the course of the disease and progressively decrease until being undetectable in the later stages due to the depletion of parietal cells	+++	++
IFAs	↑	Present in approximately 80 % of patients with pernicious anemia; more specific than PCAs (98.6 % vs. 90 %), but less sensitive (37 % vs. 81 %). Their detection becomes more pertinent during the advanced stages correlating with the atrophy stage. In the very advanced stages of A-CAG, IFAs disappear together with the disappearance of PCAs, due to the significant depletion of parietal cells	+	+

observed between PCAs titers and elevated basal serum G17.

Another study investigated the changes in serum levels of PCAs in 25 patients with autoimmune thyroid disease during a five-year follow-up, using an ELISA method [59]. At baseline, all patients were clinically asymptomatic for A-CAG and were not affected by other autoimmune diseases; 11 of them had hypergastrinemia, 20/25 patients showed an increase in PCAs concentration compared with the baseline levels (mean increment 40 %, from 58.6 ± 21.1 U/mL base level to 81.5 ± 36.8 U/mL) and five subjects showed a 30 % decrease (from 178.0 ± 68.7 U/mL to 124.4 ± 53.1 U/mL). Five years later, six subjects (24 %) who were PCAs-positive at the time of enrolment developed histologically diagnosed A-CAG.

Recently, Nishizawa et al. retrospectively classified 44 patients with A-CAG into early (diffuse infiltration of lymphocytic and plasma cells or nested in the deep layer of the mucosa), florid (severe lymphocytic infiltration, disappearance of the fundic glands, a high degree of atrophy in the oxyntic mucosa), or end-stage (severe atrophy of the oxyntic mucosa) on the basis of pathological features. The mean serum PCA titers were 480 ± 226 U in the early phase, 220 ± 235 U in the florid phase, and 150 ± 152 U in the end phase at the beginning of the study (cutoff <10 U), demonstrating that at the end stage they significantly lowered than those in the early and in the florid stage. Additionally, there was a stepwise decrease in serum gastrin levels from the early phase to the end phase [46,79]. According to that hypothesized by Tozzoli [59], the authors indicated that the titer of PCAs could fall following the progressive destruction of parietal cells and the disappearance of the proton pump as the target autoantigen.

Different results were, however, obtained by Guo and coworkers [75], who prospectively followed 16 A-CAG patients (eight men and eight women; five at the early stage, ten at the florid stage, and one at the end stage) at the baseline endoscopy (T1) and at least one follow-up endoscopy (T2, T3) for a mean time of 4.5 years (range: 2–7). In this study, serum PCAs were initially evaluated via indirect immunofluorescence using rodent stomach tissue and through anti-H+/K + -ATPase-specific automated fluorescence enzyme immunoassays and positive PCAs sera were quantified by automated fluorescence enzyme immunoassay. Ten of the sixteen patients showed a decrease in PCAs levels from the baseline to the last follow-up time point, but only two showed progression of the disease from the early stage to the florid stage, and one progressed from the florid stage to the end stage. None of the five patients with stable or decreasing PCAs levels showed changes in the stage of their disease. Overall, fluctuations in PCAs levels were modest. The median level of PCAs at the last follow-up time point did not show a significant decline compared with the level at the baseline endoscopy. The authors concluded that PCAs levels might remain stable during the disease for up to 7 years and were not severely affected by the stage of the disease.

Inconsistency in the findings obtained by Nishizawa et al. and Guo et al. might be due to the differences in the disease phases (4.6 % at the early stage, 25.0 % at the florid stage, and 70.4 % at the end stage for Nishizawa et al.; 31.2 % at the early stage, 62.5 % at the florid stage, and 6.3 % at end stage for Guo et al.), in the patient ages (65.0 ± 12.4 years for Nishizawa; 55.8 ± 13.1 years for Guo et al.), and mean follow-up times (2.5 years for Nishizawa et al. and 4.5 years for Guo et al.).

These conflicting data once again indicate that the clinical practice of monitoring A-CAG exclusively only on the basis of histological data or on histological data and the determination of PCAs should be reviewed, suggesting the integration of these two parameters with an evaluation of gastric function through measurements of biochemical markers (PGI, PGI/PGII, G17).

In a 5-year prospective follow-up study, Alonso et al. [80] determined the temporal evolution of serum PGI and PCAs in 168 patients with T1DM (87 men, 81 women, aged 31 ± 9.3 years) attending an endocrinology outpatient clinic. The author demonstrated that monitoring PGI together with PCAs for the follow up of T1DM has some utility, since the association of both tests better identified patients with a higher risk of decreased vitamin B12 levels during their follow-up.

As previously described, the destruction of parietal cells leads to a reduction in the secretion of gastric acid, thereby triggering negative feedback regulation in the antrum, resulting in increased serum levels of G17 [13]. G17 has the potential to stimulate the proliferation of enterochromaffin-like cells culminating in the development of neuroendocrine tumors [81]. Among a cohort of 135 Chinese patients diagnosed with autoimmune gastritis, 54.0 % had a gastric tumor or a precancerous gastric lesion; specifically, 37.0 % had multiple type 1

gastric neuroendocrine tumors, 11.1 % had gastric hyperplastic polyps exhibiting neoplastic transformation, 5.9 % had high-grade dysplasia or adenocarcinoma, and 3.7 % had low-grade dysplasia or adenoma [82]. In a Japanese cohort of 245 A-CAG patients, the prevalence was 11.4 % for type 1 neuroendocrine tumors (28/245) and 9.8 % (24/245) for adenocarcinomas [83]. However, a recent long-term clinical observation showed that A-CAG does not increase the risk of gastric cancer compared with that in the general population, suggesting that the previously reported increased risk may be attributed to undetected concurrent Hp infections [84]. The prognostic histological staging of the Operative Link for Gastritis Assessment (OLGA) highlighted how the risk of developing gastric cancer is higher for more advanced stages (II, III, and IV) compared with that for lower stages (0 and I), establishing a cutoff for the development of cancer between stage I and stage II; the same stratification could also be achieved through a serological evaluation of G17, which significantly increased when passing from low to advanced stages [84].

In a very interesting recent prospective single-center study, Miceli et al. [73] presented the results obtained across a 18-year follow-up study conducted on 498 A-CAG patients classified based on potential (n = 96), early (n = 63), florid (n = 64), severe (n = 263), and complicated stages (the last was defined as the presence of enterochromaffin-like cell dysplasia, type I neuroendocrine tumor, low-grade or high-grade non-endocrine dysplasia/glandular intraepithelial neoplasia, or adenocarcinoma). Patients were characterized based on immunologic, clinical, and histopathological features. The authors confirmed the hypothesis that PCAs, when present, are a true marker of potential A-CAG in many cases, as the rate of evolution over time into overt A-CAG was substantial (10.8 per 100 persons/year), but tended to fluctuate over the course of the disease for no apparent reason and irrespective of the stage of the disease. However, serum G17 turned out to be a much more reliable marker of A-CAG evolution from the potential stage to an overt stage; higher levels of G17 were associated with a more severe stage, possibly reflecting the extent of mucosal damage. In this cohort, a regression to milder lesions was never noted.

Concerning the natural history of histopathological progression, the authors confirmed that, across a longer follow-up time, A-CAG is a steadily progressive disease with no cases of atrophy regression. However, the progression towards overt adenocarcinoma was demonstrated to be virtually absent, even if the risk of developing neuroendocrine tumors was quite high, especially in patients at the severe stage. In all cases, both neuroendocrine tumors and dysplasia had an excellent prognosis because none of the patients died. These findings were similar to those of Rugge, which demonstrated that A-CAG, on its own, is not a significant precursor of gastric adenocarcinoma and clarified the relationship of A-CAG with gastric adenocarcinoma versus gastric carcinoids (also described as gastric neuroendocrine tumors, gNET). Considering a cohort of 211 selected patients (only PCAs-positive and Hp-negative), he observed an increased incidence of endocrine cell-like carcinoids only, concluding that, in the absence of Hp infection, the risk of adenocarcinoma was not significant for A-CAG [84].

To explain why PCAs-positive and Hp-negative patients failed to demonstrate increases in adenocarcinoma, Goldenring observed that it is necessary to investigate the precancerous milieu and its influence on gastric lineages. In A-CAG, pyloric or pseudopyloric metaplasia is more commonly observed than intestinal metaplasia. Since pyloric metaplasia is considered a direct response to significant gastric mucosal injury, this feature could be considered predominantly reparative. Moreover, when intestinal metaplasia is present, it is more likely to manifest as complete, rather than incomplete, intestinal metaplasia; the latter is considered the lesion with the highest risk of progressing to adenocarcinoma. Finally, although A-CAG is characterized by prominent lymphocytic infiltration, the lack of macrophages may lead to a more benign pattern of metaplasia. Different considerations are required, however, when A-CAG is associated with chronic Hp infection, as this condition confers a higher risk of adenocarcinoma [85].

As suggested by Miceli, despite the risk of developing overt gastric neoplasia being very rare even in long-term follow-up, A-CAG has to be considered a steadily progressive disease with no regression of atrophy. Therefore, high-risk categories should be serologically screened. The longer observation of these patients may still be necessary for assessing the very long-term (>20 years) risk of developing neoplastic complications, and the correct timing of follow-up should be tailored on an individual basis, taking other potential risk factors for gastric cancer into account (Table 1).

7. Conclusions and future directions

A-CAG is an important condition that involves the destruction of the gastric oxyntic mucosa through the autoimmune-mediated loss of parietal cells. Unfortunately, delays in diagnosis are frequent due to the indolent course and to the sub-clinical presentation especially in the early stages (Fig. 1).

Although PCAs are considered a useful diagnostic marker in gastric autoimmune conditions, their utility for predicting the prognosis of A-CAG remains an object of debate and contention. The precise role of this serological marker, associated with parameters of gastric function, warrants further prospective studies with larger cohorts and longitudinal follow-up data. By associating PGI with PCAs for diagnosis and using G17 for follow-up, a much more complete picture of gastric function would be obtained, thus allowing for the presence of autoantibodies to be correlated with the state of the gastric mucosa and the progression of damage (Table 2).

Even though most recent studies have emphasized that A-CAG is a progressive disorder with almost no risk of gastric adenocarcinoma development, patients with gastric atrophy should be monitored because they carry a high risk of this condition evolving into neuroendocrine (carcinoid) tumors.

CRediT authorship contribution statement

Maria Piera Panozzo: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Antonio Antico:** Writing – review & editing, Investigation, Data curation. **Nicola Bizzaro:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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