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The changing face of chronic autoimmune atrophic gastritis: an updated comprehensive perspective

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ABSTRACT

Chronic autoimmune atrophic gastritis (CAAG) is an organ-specific autoimmune disease, which affects the corpus–fundus gastric mucosa. Although it has been described for several years, the real pathophysiological mechanisms, the natural history and the possible neoplastic complications are not completely known. Atrophy of the gastric mucosa is the endpoint of the chronic processes, with the loss of glandular cells and their replacement by intestinal-type epithelium, pyloric-type glands, and fibrous tissue. As a consequence, hydrochloric acid, pepsin and intrinsic-factor is impaired resulting in pernicious anemia. The exact causal agent is not yet known, but both genetic and environmental factors seem to play a decisive role.

Moreover, the clinical onset may assume different characteristics; differently from what previously observed, recent evidence has reported the onset of CAAG at a younger age, frequently with iron deficiency anemia or upper gastro-intestinal symptoms.

The diagnosis of CAAG might be challenging and usually requires the combination of clinical, serological and histopathologic data; moreover, CAAG patients are often misdiagnosed as refractory to HP eradication therapy, probably because achlorhydria might allow urease-positive bacteria other than *H pylori* to colonize the stomach, causing positive ^{13}C-urea breath test results.

However, biopsy is the most reliable method to evaluate the presence of metaplastic atrophic gastritis. In order to assess the severity of gastric atrophy and intestinal metaplasia, OLGA and OLGIM staging systems have been proposed and seem to correlate with the risk of developing gastric adenocarcinoma. Indeed, CAAG represents a pre-neoplastic condition, as patients with CAAG are very likely to develop either type-1 gastric neuroendocrine tumors and gastric adenocarcinomas, as well as several other neoplastic diseases. To date, the need, the intervals and cost-effectiveness of endoscopic/histological surveillance for patients with CAAG/pernicious anemia are yet to be established.

1. Introduction

Chronic autoimmune atrophic gastritis (CAAG) is an organ-specific autoimmune disease that affects the corpus–fundus mucosa of the stomach. The onset of autoimmune gastritis is marked by circulating parietal cell antibodies against the adenosine triphosphate (ATPase) H/K (parietal cell antibodies, PCA) and antibodies to the intrinsic factor (anti-IF). The inflammatory infiltrate of the mucosa, represented by T and B lymphocytes and macrophages, causes the destruction of the native gastric glands, both specialized parietal and zymogenic cells, with the consequent development of intestinal metaplasia or atrophy, deficiency of intrinsic factor and chlorhidric acid, thus leading to hypergastrinemia, decreased blood levels of pepsinogen I(PG-I) and enterochromaffin-like cell (ECL) hyperplasia [1]. CAAG and pernicious anemia (PA) have a prevalence of 2% and 0.15%–1%, respectively, with an age-dependent increase [2]; the annual incidence of CAAG is 25 new cases/100,000 people [3], with a higher frequency in patients with other autoimmune diseases, in particular diabetes mellitus and autoimmune thyroid disease [4]. CAAG is more common in women (F: M ratio of 3:1) and in subjects aged over 60 years, although an increased incidence in the population aged between 35 and 45 years has been recently observed by a recent Swedish prospective study [5].

2. Pathophysiology

Most of the knowledge about the pathogenesis of CAAG comes from

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studies of experimental models. The exact causal agent is not yet known, but both genetic and environmental factors seem to play a decisive role. Many possible confounders or contributing factors may interfere, also considering the low prevalence of CAAG: *e.g.* the frequent co-presence of atrophic gastritis related to *Helicobacter pylori* (*H. pylori*) and the often late diagnosis. However, as observed by a recent study on 404 patients treated for *H. pylori* (HP) infection [6], CAAG patients are often misdiagnosed as refractory to HP eradication therapy, probably because achlorhydria might allow urease-positive bacteria other than *H. pylori* to colonize the stomach, causing positive ^{13}C-urea breath test (^{13}C-UBT) results.

Although it is not completely clear whether the antibodies PCA and anti-IF play a definitive pathogenic role in CAAG, gastric H/K-ATPase reactive CD4 T-cells are the major drivers of the underlying autoimmune mechanisms of the disease. The T-mediated chronic stimulation of B lymphocytes leads to the local production of PCA and anti-IF [7]. Several reports suggest that parietal cell death depends on Th1 CD4 T-cells and Fas/Fas-ligand, either through the interaction between infiltrating CD4 T-cells with gastric parietal cells that have up-regulated Fas expression or through homotypic interactions between parietal cells. [8]. Some observations suggest some genetic predisposition in humans and two studies have suggested an association with HLA-DRB103 and HLA-DRB104. [9]. The molecular mimicry between *H. pylori* antigens and gastric H/KATPase has been invoked as a pathogenic mechanism, because of the high homology observed between the beta subunit of *H. pylori* urease and the beta subunit of ATPase [10]. Moreover, the chronic self-aggression of gastric parietal cells causes hypo-achlorhydria, which alters the somatostatin-mediated negative feedback that regulates gastrin secretion by the antral G-cells [11].

3. Association of autoimmune gastritis with other autoimmune diseases

Patients with CAAG have a 3–5 times higher risk than the general population of developing further autoimmune diseases, such as chronic autoimmune thyroiditis, type-1 *diabetes mellitus* [5,12,13], vitiligo [14], Addison's disease [15], *myasthenia gravis* [16], oral erosive lichen planus. The list of autoimmune diseases associated with CAAG and the strength of this association have been reported in Table 1.

The most common association is with autoimmune thyroiditis

Table 1
Autoimmune diseases associated with CAAG. The strongest association is found with autoimmune thyroiditis and type-1 diabetes mellitus. (CAAG: chronic atrophic autoimmune gastritis; PSC: primary sclerosing cholangitis; PBC:primary biliary cholangitis).

Autoimmune diseases associated with CAAG	Stenght of association
Chronic autoimmune thyroiditis (Hashimoto's thyroiditis) and Graves' disease	+ + + + (some cohort studies, two cross-sectional studies and two case-control studies)
Type-1 diabetes mellitus	+ + + (one case-control study and some cohort studies)
Vitiligo	+ + (one cohort study and some case reports)
Alopecia	+ + (some cohort studies)
Celiac disease	+ + (some cohort studies)
Myasthenia gravis	+ (only case reports)
Connective tissue disease	+ + (one cohort study and case reports)
Primary biliary cholangitis	+ + (case reports and one cohort study)
Primary sclerosing cholangitis	+ (only case reports)
Autoimmune hepatitis	+ (only case reports)
Addison's disease	+ (only case reports)
Primary ovarian failure,	+ (only case reports)
Primary hypoparathyroidism,	+ (only case reports)
Lambert–Eaton syndrome	+ (only case reports)
Oral erosive lichen planus	+ (only case reports)

("thyrogastric autoimmunity"). Indeed, CAAG has been reported in 24%–35% of patients with autoimmune thyropathies [17–19], especially Hashimoto's thyroiditis, with a higher prevalence (up to 45%) in older patients [4,20]. In a study by Lahner et al. [21] on 319 CAAG patients, the risk factors for autoimmune thyroid disease were: female sex, presence of PCA and presence of metaplastic atrophy; at multivariate analysis an increased risk of having a concurrent autoimmune disease was associated with the serum gastrin level, serum chromogranin A level and the presence of ECL cell hyperplasia. Moreover, up to 82% of patients with autoimmune thyroiditis presented anemia, both as PA and iron-deficiency anemia [4]. The pathogenic mechanisms responsible for the clinical relationship between autoimmune thyroiditis and CAAG remains to be elucidated: these two disorders present some intriguing similarities. Indeed, the thyroid gland and stomach share a common embryologic origin, *i.e.* the primitive gut; furthermore, gastric mucosal and thyroid follicular cells both show the ability to concentrate and transport iodine across the cell membrane and, besides its role for the synthesis of thyroid hormones, iodine also regulates the proliferation of gastric mucosal cells. Moreover, in both these autoimmune disorders the Fas up-regulation has been observed, thus triggering apoptosis by binding Fas-ligand on infiltrating T-cells [8].

As concerned type-1 *diabetes mellitus*, it has been observed that 6%–10% of patients with insulin-dependent diabetes present a concomitant CAAG [4,12], with an age-dependent increase of prevalence of autoimmune gastritis [22]; the risk effect of the DR3-DQ2, DRB1*0404 (in males) and DR3-DQ2/DR4-DQ8 genotypes on the development of CAAG has emerged from two recent large studies [22,23]. Furthermore, anti-glutamate decarboxylase autoantibodies were predictive of co-existing PCA positivity [23].

CAAG may *co*-exist with polyglandular autoimmune (PGA) syndrome: indeed, it occurs in 10%–15% of patients with PGA type-1 syndrome (hypoparathyroidism, Addison's disease, *diabetes mellitus*, and muco-cutaneous candidiasis) and in 15% of type-3 PGA patients (with *diabetes mellitus* and autoimmune thyroid diseases) [24].

A significant association with vitiligo, alopecia, celiac disease, Addison's disease, *myasthenia gravis*, connective tissue diseases and autoimmune hepatitis have also been reported [25–30].

Zhang et al. [31] have reported a quite high prevalence of anti-nuclear (29.2%) and anti-mitochondrial antibodies (3.5%), although no specific clinical manifestation (fatigue and/or itch) was seen in all the patients and only two of them had abnormal liver biochemistry (light elevated alkaline phosphatase and/or gamma-glutamyl transpeptidase). In a study by Kalkan et al. [32] on a cohort of 320 CAAG patients, 53% presented additional autoimmune diseases, multiple in 11% of them. Autoimmune thyropathies were the most common concurrent disease (39%); other concurrent autoimmune diseases were: rheumatoid arthritis (9%), lupus (6%), celiac disease (3%), autoimmune hepatitis (3%) and ankylosing spondylitis (2%).

Moreover, another study on 157 patients affected by primary biliary cholangitis (PBC) [33] detected a significantly higher positivity of PCA and/or IF-antibodies in PBC (32%) compared to AIH (11%), PSC (0%), although a definite diagnosis of CAAG was made in only 14%, possibly because of a cross-reaction of AMA pattern and PCA on rat stomach sections. Therefore, at least in these cases, the first-line screening for PCA and IF- antibodies should be done by IgG-specific ELISAs.

4. Clinical manifestations

CAAG may be asymptomatic or characterized by the presence of non-specific gastro-intestinal symptoms. However, some haematological, neuropsychiatric and gastroenterological manifestations can be observed. The most common initial findings were haematological disorders (37% of cases), followed by a histology positive for gastritis (34%), whereas in < 10% of cases the clinical suspicion of CAAG was determined by the concomitant presence of other autoimmune diseases, neurological symptoms or a positive family history [34]. The list of the

Table 2
Main clinical manifestations of CAAG. (CAAG: chronic atrophic autoimmune gastritis).

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

possible clinical manifestations of CAAG have been summarized in Table 2.

Older patients often tend to have vitamin B_{12} deficiency, whereas for young patients the symptoms that prompted investigation were mainly upper gastro-intestinal symptoms or iron-deficiency anemia. Furthermore, polyautoimmunity, along with delayed gastric emptying, are more frequently observed in old patients [34].

Among the hematologic manifestations PA, which is characterized by macrocytic anemia with B_{12} deficiency that responds to parenteral B_{12} supplementation, is present in the 54%–62% of cases. However, macrocytosis and reticulocytopenia are absent in 30% of the cases and non-anemic macrocytosis or spuriously high or normal cobalamin levels can be detected in up to 35% of cases [35,36], because of the interference of the immunofluorescence assays with the automated assays [37]. In those cases the diagnosis of PA is made by elevated plasma homocysteine and methylmalonic acid (MMA), positive IF and/or PCA and/or megaloblastic bone marrow changes. Moreover, about 1.5% of patients can present Coombs-negative hemolytic anemia due to ineffective erythropoiesis and 2.5% of patients might present pseudothrombotic microangiopathy, which is characterized by hemolysis, thrombocytopenia and schistocytosis, because of erythroblast cytoskeletal fragility [38]. More rarely, PA may debut as a bone marrow failure with pancytopenia or as a sideroblastic anemia, reversible after cobalamin supplementation, or as a "pseudo-leukemia" mimic syndrome: the presence of hyper-segmented neutrophils is suggestive of cobalamin deficiency, although it has not been consistently described in the literature [36].

Interestingly, iron deficiency anemia may precede the appearance of B_{12}-deficient anemia, especially in young female patients, in the 35%–58% of patients [39]. Indeed, Hershko et al. [40] have observed the presence of refractory iron deficiency anemia in 27% of patients with CAAG. More recently, the same authors have found that iron deficiency anemia was the presenting feature in 83 of 160 CAAG patients (52%), which suggests that iron deficiency anemia might be the most common haematological presentation of this condition.

As regards gastrointestinal symptoms, they are present in > 50% of patients, as observed by a recent study by Carabotti et al. [41]. The presence of dysmotility-type dyspepsia has been reported alone in 70% or associated to reflux symptoms in 17.7% of symptomatic patients. Age < 55 years (OR 1.6, CI: 1–2.5), anemia (OR 3.1, CI: 1.5–6.4) and absence of smoking (OR 2.2, CI: 1.2–4) were independent factors associated with dyspepsia. Symptomatic patients were mostly females, significantly (*i.e.* about 5 years) younger, in comparison to the asymptomatic ones. No significant differences were found between symptomatic and asymptomatic patients as concerns the presence of iron deficiency anemia, positivity to gastric autoantibodies, prevalence of *H. pylori* infection, the concomitant presence of autoimmune disorders and the grading of gastric atrophy, whereas PA was significantly more frequent in the asymptomatic group.

A study by Kalkan et al. [42] on 165 CAAG patients presenting with dyspepsia has observed delayed gastric emptying at gastrointestinal scintigraphic study in 80% of cases, probably because of alterations of the antral contractions or hypergastrinemia, which stimulates antral contractile activity. Furthermore, as observed in several studies [28,41,43], up to 25% of CAAG patients have reflux symptoms as confirmed at esophageal pH-impedance monitoring, which are probably related to the presence of non-acid reflux.

Finally, as concerns the neuropsychiatric manifestations, they may precede the appearance of haematological manifestations and generally improve after vitamin B_{12} supplementation, especially if carried out early [44]. B_{12} deficiency can cause peripheral neuropathy (25% cases) or sub-acute degeneration of the posterior and lateral columns of the cervical and thoracic spinal segments, with consequent alteration of proprioception, vibratory sensitivity and distal paraesthesia. Optic nerve neuropathy is less frequent and leads to progressive bilateral blindness. Autonomic abnormalities and memory loss are less common at the time of diagnosis and occur in 1%–2% of cases. In a retrospective case series of 369 patients with documented cobalamin deficiency, 143 had neurological disorders attributable to it: the mean corpuscular volume was normal in > 25% of cases and only 19% of patients were severely anemic [45].

In addition to neurological manifestations, psychiatric disorders are also reported in CAAG patients, such as: mania, depression, obsessive-compulsive disorder, psychosis and cognitive impairment.

5. Laboratory diagnosis

Over the last two decades, there have been increasing levels of awareness and attention on CAAG pathogenesis [46] and its clinical [28], laboratory [1,47–49] and histopathological diagnosis [50]. The diagnosis of CAAG might be challenging and usually requires the combination of clinical, serological and histopathological data [51].

PCA [52] is positive in the 85%–90% of CAAG patients, with suboptimal specificity since they can be detected in other autoimmune disease, *e.g.* type-1 diabetes, Hashimoto's thyroiditis [53]. PCA identification can be made by immunofluorecence or ELISA, the latter being 30% more sensitive [52]. Of interest, PCA may rise, peak and fall over time in the natural history of CAAG, following the progressive destruction of the gastric mucosa and consequent loss of target auto-antigen, thus PCA may disappear in the late stages [52]. In case of further doubts, the detection of anti-IF antibodies, identified by ELISA, can increase PCA diagnostic accuracy [1], thanks to their high specificity (98.6%) despite their low sensitivity (60%) [47,48]. Furthermore, Antico and colleagues have demonstrated that IF positivity has a good correlation with gastric atrophy [54]; moreover, these authors have proposed the so called "serological biopsy", which is a combination of measurements of PCA, IF, serum gastrin and anti-*H. pylori* antibodies [53]. Many studies have described serum biomarkers for gastric atrophy, such as pepsinogen 1 (P1), pepsinogen 2 (P2), P1/P2 ratio, and serum gastrin levels, in order to diagnose gastric atrophy without endoscopic biopsy [54,55]. The concordance of these serum biomarkers with gastric atrophy at histological specimen was excellent: the P1/P2 ratio has showed the highest sensitivity (96%) and the highest negative predictive value (97.7%) towards the diagnosis of gastric atrophy; while P1 has showed the highest specificity for gastric atrophy diagnosis [55]. Furthermore, Miceli E et al. [51], in a study involving 139 CAAG patients and 510 controls, have proposed a screening test, based

on the mean corpuscular volume and hemoglobin, B_{12}, 17-gastrin and chromogranin A (CgA) levels, with the goal of simplifying CAAG diagnosis, both in the gastroenterological setting and in general practice. They have developed a global score and a simplified score (based on the mean corpuscular volume and hemoglobin and gastrin levels) to discriminate CAAG patients, with sensitivity, specificity, positive predictive value and negative predictive value of 88.4% and 85.6%, 94.1% and 95.3%, 80% and 83.2%, 96% and 96%, respectively. Even though the authors have showed the good diagnostic performance of their simplified score in the validation cohort (AUC-ROC 0.85, 95% CI 0.74–0.95), their screening test has been so far poorly used in clinical practice.

Moreover, the measurement of the CgA levels has been suggested for the diagnosis of CAAG, ECL-cells hyperplasia and gastric carcinoids, as they seem to correlate with the degree of ECL hyperplasia in CAAG patients. However, CgA levels can be affected by other various neoplastic and non-neoplastic conditions, such as chronic inflammatory diseases, inflammatory bowel diseases, hepatocellular carcinomas, non-alcoholic fatty liver disease, renal insufficiency, chronic use of proton pump inhibitors [56,57].

6. Endoscopic findings

In the diagnostic process of CAAG, endoscopy is usually carried out to take gastric biopsies and obtain histopathological diagnosis [58]. The endoscopic appearance of CAAG may not be different from the healthy situation during the early disease stages, whereas flattened rugal folds and sub-mucosal vessels may be visible in case of extensive atrophy (Fig. 1) and pseudopolyps or polyps (hyperplastic or adenomatous) might be present (Fig. 2) [59,60]. Unfortunately, the macroscopic endoscopic findings have several limitations as a diagnostic tool, because of their low sensitivity and specificity and inter-observer variability.

Moreover, the recent endoscopic advancements (*i.e.* narrow-band imaging, magnifying endoscopy, autofluorescence imaging and confocal microscopy) allow the suspecting of CAAG based on mucosal endoscopic aspect [60]. For instance, it has been shown that normal gastric corpus and fundus mucosal microvessels are characterized by the presence of a subepithelial capillary network resembling honeycomb and collecting venules in regular shape and appearance: such findings are not seen in patients with atrophic gastritis [61]. High-resolution endoscopy can be a useful tool to target and take biopsy from the atrophic mucosa, thus increasing the diagnostic yield [58]. As a final remark, Yagi and colleagues have tried to describe a specific aspect of atrophic gastric mucosa of the corpus using magnifying endoscopy: they reported 3 cases with closely arranged small round and oval pits in the atrophic mucosa; histological specimens, PCA and high gastrin levels then confirmed that diagnosis [62].

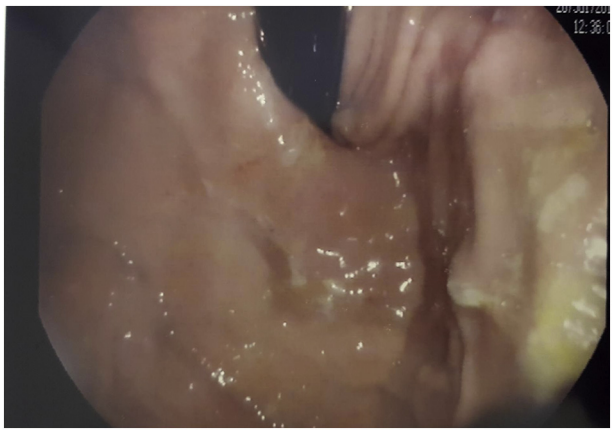

Fig. 1. Endoscopic appearance of the gastric fundus showing visible sub-mucosal vessels in a patient with extensive atrophic autoimmune gastritis.

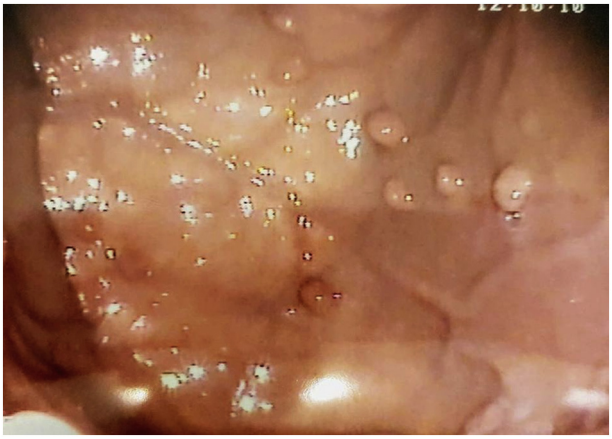

Fig. 2. Some *polyps, all sessile and with a diameter* < 1 cm, in the gastric fundus of a CAAG patient. Histology showed they were gastric neuroendocrine neoplasms.

However, endoscopic findings are not sufficient to diagnose CAAG. According to the updated Sydney recommendations, five biopsy samples should be obtained: two from the corpus, two from the antrum and one from the *incisura angularis* [63]. To further improve the diagnostic yield of gastric biopsies, Park and colleagues have suggested to take further samples from lesions (ulcer, polyps, nodules) and the mucosa adjacent to such lesions [60].

7. Histology

Biopsy is the most reliable method to evaluate the presence of metaplastic atrophic gastritis, but in case of severe inflammation it is difficult to assess the presence of atrophy.

The histopathological changes of autoimmune atrophic gastritis can be divided into three evolving phases [64]. The earliest histological alterations include the patchy destruction of oxyntic glands and the infiltration of the lamina propria by plasmacells and lymphocytes, with a mainly top-down gradient. The pseudo-hypertrophy of the remaining parietal cells like that seen in patients on proton-pump inhibitors (PPI) therapy may also be present [65,66]. In a later phase (florid), a dense infiltrate of lymphocytes and plasmacells in the lamina propria and atrophic glandular alterations become clearly visible, with the replacement of the native population of parietal cells by a new phenotype of clear, muco-secreting epithelia, with the phenotype of antral glands ("oxyntic antralization") [66]. These features are sufficiently distinctive to diagnose autoimmune atrophic gastritis, particularly if the antrum is not inflamed or atrophic. Finally, advanced CAAG is characterized by "oxyntic mucosa desertification" (*i.e.* the replacement of the oxyntic glandular units by fibrosis of the lamina propria), foveolar hyperplasia with underlying microcystic change and the formation of hyperplastic and inflammatory polyps. Pseudopyloric, pancreatic and intestinal metaplasia becomes widespread and inflammation is generally minimal.

Furthermore, other common features are: the hyperplasia of the muscularis mucosae, oxyntic pseudo-polyps and ECL-cells hyperplasia, which is caused by chronic hypergastrinemia and can be of a simple type, linear, micronodular and, in the most severe form, of macronodular type, according to the Solcia classification [67].

In cases of concurrent *H. pylori* infection, the antral mucosa may feature the classic spectrum of *H. pylori*-related lesions, so that CAAG can be only diagnosed thanks to its specific serological profile (anti-parietal cell and anti-intrinsic factor autoantibodies) [50].

In up to one third of cases the diagnosis of CAAG is clinically unsuspected [68]: a prominent eosinophil infiltrate, chronic inflammation associated with lymphocyte infiltration into the basal glandular

epithelium of at least one gland, thickening of the muscularis mucosae to at least twice as normal size and gland architectural irregularity are more common in CAAG patients than in HP-related gastritis and are helpful when biopsy site and/or clinical history are uncertain. Moreover, the finding of lymphoid aggregates has no diagnostic use in the differential diagnosis between CAAG and HP-related gastritis, since they are often seen in CAAG patients as well.

The Sydney system and Updated Sydney system were primarily designed to provide standardization for reports of gastric biopsies [63,69]. In order to assess the severity of gastric atrophy, OLGA staging has been proposed, which distinguishes four stages of severity for gastric atrophy, by scoring atrophy histologically in both oxyntic and antral/angular biopsy samples. Stages III and IV are associated with a greater risk of developing gastric cancer [69–71]. A recent work by Rugge et al. observed a tendency to OLGA stage progression in 22% of cases [72].

Finally, an alternative staging system (OLGIM) has been proposed: OLGIM considers only IM (intestinal metaplasia) for the staging of gastric atrophy, but it can underestimate the grading of atrophy since it excludes both non-metaplastic and pseudopyloric metaplasia from the atrophy score.

7.1. Mucosal atrophy

Gastric mucosal atrophy may present as the replacement of the glandular units by fibrotic expansion of the lamina propria or by metaplastic glands. Within the oxyntic mucosa, metaplasia [69] can be distinguished in two types. The first type is pseudo-pyloric metaplasia (or spasmolytic polypeptide-expressing metaplasia, SPEM), which is identified by the presence of mucosa with an antral phenotype, stains positive for PG-I and is anatomically in a region where the corpus would be expected [73]. SPEM develops in the oxyntic glands from mucus-secreting cells similar to the antral cells, but from which they are differentiated by the presence of PG-I. The second type is intestinal metaplasia (IM), which is characterized by the replacement of foveolar and/or glandular epithelium by intestinal epithelium. It is divided into two subtypes: small intestine (type I or incomplete IM) containing epithelium of the small intestine with a brush-like band, which expresses sialomucins with all types of cells (*i.e.*, Goblet, Paneth); colonic-type (type II and type III or complete IM), with no brush-shaped band. As a matter of fact, there is also a third type called pancreatic acinic cell metaplasia, which is rare.

In the angulus, however, it is not easy to distinguish between non-atrophic antral gastritis and atrophic gastritis with pseudopyloric metaplasia: therefore, at this level only the presence of intestinal metaplasia is indicative of atrophy of the oxyntic mucosa [72].

7.2. Neuroendocrine cells hyperplasia

Hypergastrinemia triggers ECL cells proliferation. Linear ECL cell hyperplasia, characterized by five adjacent chromogranin-expressing ECL cells lining the glandular neck region, is the earliest lesion. Micronodular hyperplasia refers to clusters of neuroendocrine cells (not exceeding the diameter of a gastric gland, *i.e.* < 150 μm) surrounded by basement membrane, whereas adenomatoid hyperplasia is represented by five or more clusters of micronodules [66]. Finally, ECL cell dysplasia refers to nodules > 150 μm in diameter without evidence of a basal membrane and may progress to micro-invasive tumors infiltrating the lamina propria: microcarcinoids if the diameter is < 5 mm or carcinoids if they have a diameter > 5 mm. A study on a transgenic mouse model has observed that progenitor cells of the oxyntic glands may promote a cell population characterized by the loss of native parietal cells marker (*i.e.* H/K-ATPase) expression, the neoexpression of neuroendocrine antigens (chromogranin A) and a phenotype consistent with entero-endocrine cells on electron microscopy [74]. These findings might explain the pathogenesis of neuroendocrine tumors associated with CAAG.

7.3. Polyps

Gastric lesions may be represented by hyperplastic polyps, pyloric gland adenomas, gastric adenocarcinoma or neuroendocrine neoplasm.

Hyperplastic polyps are meta-inflammatory proliferations of the gastric foveolar cells, are characterized by elongated and dilated hyperplastic foveolae in an edematous, hyper-vascular, inflammatory stroma. An association between hyperplastic polyps and atrophic autoimmune gastritis is well established. In these patients, the polyps are often proximally located, can present superficial erosions and are more numerous than in patients with other forms of gastritis [75]. Pyloric gland adenomas are characterized by closely-packed pyloric-type glands, lined with cubic or columnar mucus-secreting cells that express both MUC6 and concavalin A, are generally located in the oxyntic mucosa (54%) and less frequently in the cardia region. In two large series including 131 pyloric gland adenomas, one-third was present in patients with autoimmune gastritis [76]. Sometimes dysplasia may occur; moreover, cases of progression to pyloric-type gastric adenocarcinoma have been reported in up to 30% of cases. [75,77].

When gastric atrophy is extensive, the remnants of preserved oxyntic mucosa protrude into the gastric lumen as pseudopolyps, which are similar to the pseudopolyps found in patients with inflammatory bowel disease [78].

8. Neoplastic complications

CAAG represents a pre-neoplastic condition: the patients with CAAG are very likely to develop several neoplasms, in particular type-1 gastric neuroendocrine tumors (type-1 gNEN) and gastric adenocarcinomas (GA) [31,79,80]. A population-based case-control study based on the Surveillance, Epidemiology and End Results–Medicare database [80] showed that individuals with PA have a significantly increased risk of both type-1 gNEN (odds ratio, 11.43; 95% CI 8.90–14.69) and GA (odds ratio, 2.18; 95% CI 1.94–2.45). In line with these data, an Asian study has also reported an incidence of gastric cancer in CAAG patients between 1% and 3% for GA and between 1% and 7% for type-1 gNEN [81].

A recent study, which compared the human gastric microbiota in hypochlorhydric states (*H. pylori*-induced atrophic gastritis, autoimmune atrophic gastritis and proton-pump inhibitor use), has observed a relatively higher microbial diversity in CAAG patients, with samples dominated by Streptococcus, than in patients with HP-related gastritis. Indeed, gastric atrophy was associated with changes of the citric acid cycle, a bio-chemical pathway associated with gastric carcinogenesis, thus suggesting that the microbiota may be an important contributor to the development of gastric cancer [82].

Furthermore, the patients with PA seem to be at increased risk for other malignancies, in particular oesophageal squamous cell cancer, whereas they had a reduced risk for rectal cancer [79]. A recent meta-analysis [83] has indeed shown an overall relative risk (RR) of cancer of 0.68 (95% CI 0.48–0.95) among 82,257 PA patients. The PA patients had a lower RR of colorectal, breast, liver, oesophageal, lung, thyroid, ovary, non-melanoma skin and kidney cancers but had a higher RR of biliary tract cancer (1.81), multiple myeloma (2.83), Hodgkin's lymphoma (3.0), non-Hodgkin's lymphoma (2.08), and leukemia (1.56).

8.1. Gastric adenocarcinoma (GA)

The risk of developing gastric adenocarcinoma (GA) is reported for CAAG patients with an incidence range between 0% and 1.8% per year [84], although the studies available in the literature differ in terms of types of chronic gastritis, sample size and methods for the identification of GA used during the follow-up.

Song et al. have reported on a large retrospective cohort regarding

the risk factors for gastric tumorigenesis in atrophic gastritis of various types, but mainly *H. pylori*-related [85]. Extensive mucosal atrophy, differently from corpus-restricted atrophic gastritis has been linked to an increased risk of gastric cancer [86,87]. However, some recent studies [30,78] and a large systematic review by Vannella et al. [88] have reported a pooled gastric cancer incidence rate of 0.27% per person-years and an estimated nearly seven-fold relative risk of gastric cancer for pernicious anemia patients, with an escalation of neoplastic risk according to the extent and duration of atrophy [89].

Finally, in experimental mice models several pro-inflammatory cytokines have been implicated in the tumorigenesis of atrophic gastritis, including TNF-α, IL-1β, IL-6, IL-8 and IFN-γ [90,91].

8.2. Type-1 gastric neuroendocrine tumors (type-1 gNEN)

Type-1 gNENs may also arise in CAAG patients in a percentage variable from 0.4% to 7% of the CAAG patients screened by endoscopy [88]. These neoplasms are mainly owed to hypergastrinaemia, which causes enterochromaffin-like cells hyperplasia that eventually progresses to dysplasia and neuroendocrine tumors development through a multi-step process. They are well-differentiated with a low proliferative index and a generally benign behavior [92]. The data on the long-term incidence of type-1 gNENs are scant [93,94], with a reported annual incidence of 0.68% person-years [95]. The most important risk factors are: male gender, chromogranin A levels > 61 U/L and presence of intestinal metaplasia [96]. While the role of hypergastrinemia in the development of CAAG into gNEN is well established [97], the contribution of immune mechanisms is less clear, although there is evidence in other systems that pro-inflammatory cytokines, such as TNF-α, may contribute to neuroendocrine cell differentiation/hyperplasia.

9. Endoscopic surveillance

To date, the need, the intervals and cost-effectiveness of endoscopic/histological surveillance for patients with PA are yet to be definitively established.

Conventional white light endoscopy cannot accurately differentiate and diagnose pre-neoplastic gastric conditions, whereas magnification chromo-endoscopy and narrow-band imaging, with or without magnification, improve the diagnosis of gastric pre-neoplastic conditions.

As suggested by the ESGE guidelines [86] patients with low-grade dysplasia in the absence of any endoscopically defined lesion should receive follow-up within 1 year from diagnosis, whereas endoscopic resection should be considered in the presence of an endoscopically defined lesion. Patients with high-grade dysplasia in the absence of an endoscopically defined lesion should receive immediate endoscopic reassessment with multiple biopsies and follow-up at 6-month/one-year intervals.

As regards follow-up, Kokkola et al. [94], considering the relatively benign nature of type-1 gNEN in patients with PA, have concluded that it is indicated at 5-year intervals only for patients with ECL hyperplasia: the first surveillance upper endoscopy after PA diagnosis should be performed relatively soon and only PA patients with pre-neoplastic lesions and those with gastrointestinal symptoms should undergo endoscopic surveillance. Another study suggested follow-up to be at 3-year intervals only for PA patients aged < 60 years [98]. A more recent study which has compared the usefulness of 2- and 4-year follow-up for patients with CAAG, shows that the first follow-up performed 4 years after diagnosis seems to be safe and convenient as to the early detection of potentially neoplastic lesions [99].

The costs of endoscopic surveillance have been only partially assessed. A recent Italian study has assessed the costs of detecting gastric neoplasms by surveillance endoscopy in a cohort of 200 CAAG patients followed up over a mean of 7.5 years: it has observed that neoplasms were diagnosed in 19 patients out of 200, with a total number of 19 every-4-year surveillance endoscopies to be performed in order to detect one gastric neoplasm. The same study has demonstrated that, by restricting surveillance to PA patients, a reduction of the cost per lesion (€2139) would be obtained while still detecting 74% of neoplasms and that, by limiting surveillance to PA patients with OLGA stages 3 or 4, neoplasms would be detected with a further reduction of the cost per lesion (€837) [100].

10. Treatment

The treatment of PA is a lifelong replacement therapy with intramuscular cobalamin at the dosage of 1000 μg daily or every other day for a week, followed by a weekly administration for one to two months and then monthly lifelong [101]. High replacement doses, orally, of 500 to 1000 μg a day seem to be effective in case of little atrophy [102]. The cobalamin therapy reverses all abnormal hematologic changes, serum MMA and plasma homocysteine levels within the first 5 days to 2 weeks of treatment [103], with the normalization of serum cobalamin after two weeks of treatment. Macrocytosis generally disappears during the first month of treatment, whereas the normalization of hemoglobin would take longer. The neurological symptomatology response depends on the severity of symptoms and their duration before the beginning of treatment [1].

Finally, since other micronutrient deficiencies as folate or 25-OH vitamin D have been reported in CAAG patients [104], these micronutrients should be regularly checked and specific supplementation of these micronutrients is indicated in case of deficiency.

11. Conclusions

CAAG or type-A chronic atrophic (autoimmune) gastritis has changed its morphology in the recent years and alongside the more classic manifestations, other facets of the disease are now known.

The diagnosis of CAAG might be challenging and the clinical presentation may be more variable than previously thought. CAAG should also be considered in presence of other autoimmune disease, especially chronic autoimmune thyroiditis and type 1 diabetes mellitus.

As the chronic autoimmune damage typical of CAAG causes not only the progressive loss of parietal cells with subsequent vitamin B_{12} deficiency, but also a chronic histological reshaping, which can induce a precursor condition for gastric neoplasms, a specific follow-up should be set up on a long-term period and according to identified risk factors. Endoscopic surveillance, even if commonly recognized, has not been fully and firmly established in terms of follow-up intervals and duration.

Conflict-of-interest statement

No conflicting interests (including but not limited to commercial, personal, political, intellectual, or religious interests) to declare.

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