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Review

Clinical manifestations of chronic atrophic gastritis

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Summary. Although the actual prevalence of chronic atrophic gastritis is unknown and it is probable that this entity goes largely underdiagnosed, patients in whom diagnosis is established usually present advanced stages of disease. Destruction of parietal cells, either autoimmune-driven or as a consequence of Helicobacter pylori infection, determines reduction or abolition of acid secretion. Hypo/achloridia causes an increase in serum gastrin levels, with an increased risk of the development of neuroendocrine tumors. Microcytic, hypochromic anemia frequently precedes the development of megaloblastic, vitamin B12-associated anemia. Moreover, vitamin B12 deficiency,may cause elevation of homocysteine, with an increase in the cardiovascular risk, and may be associated with neurological manifestations, mainly characterized by spinal cord demyelination and atrophy, with ensuing sensory-motor abnormalities. Gastrointestinal manifestations seem to be associated with non-acid reflux and tend to be non-specific. (www.actabiomedica.it)

Key words: gastritis, pernicious anemia, neuropathy, megaloblastic

Chronic atrophic gastritis (CAG) is the final consequence of an inflammatory process that ultimately leads to loss of appropriate mucosal glands. This histological alteration may be due to an autoimmune-mediated reaction directed towards parietal cells or their components, or may be associated to infection with *Helicobacter pylori* (1). To date, no universally accepted criteria are available to define autoimmune gastritis and to definitively distinguish this clinical entity from chronic, *H. pylori*-driven, multifocal atrophic gastritis. Features traditionally used to distinguish either etiology, such as positivity to intrinsic factor and parietal cell antibodies, presence of enterochromaffin-like cells, and absence of active *H. pylori* infection, have all been reported to be present in similar proportions in patients with body-restricted atrophic gastritis (the classical histological feature of autoimmune gastritis) and those with antral and body atrophic gastritis (more commonly attributed to *H. pylori* infection) (2, 4) thus, the specific features associated with autoimmune gastritis are far from being well defined.

There are two principal methodological approaches to assess this condition, namely serological studies using markers of gastric function (pepsinogen I, or pepsinogen I/pepsinogen II ratio, with or without the addition of gastrin-17 and antibodies against *H. pylori*) or invasive studies requiring histological analysis of biopsy samples taken in the course of upper esophagogastroduodenoscopy, the latter constituting the gold standard for establishing the diagnosis.

A standardized and validated method to stratify and grade severity and distribution of atrophy, the Operative Link on Gastritis Assessment (OLGA) system, allows the classification of patients in 5 groups from stage 0 to stage IV (5). More severe stages of atrophy (OLGA III and IV), characterized by extensive atrophy of the antrum and/or of the oxyntic mucosa, are associated with an increased risk of developing gastric

neoplasms(6). Notwithstanding a reduction in the incidence of this tumor, it remains an important cause of death associated with cancer, with a 5-year survival of 32.4% in Italy. (7, 8) Due to its high mortality and its silent presentation, the identification of a subgroup of patients who are at higher risk is important, as in these patients endoscopic surveillance is warranted. Thus, early identification of patients with CAG and their follow-up according to the risk of progression allows for early identification of neoplasms and reduction in gastric cancer mortality.

Destruction of parietal cells in CAG leads to a reduction or abolition of acid secretion, which can lead to the development of clinical extra-digestive manifestations that might aid in the identification of these patients, including iron deficiency, which can be associated with microcytic anemia. Vitamin B12 deficiency, due to a reduction of intrinsic factor produced by parietal cells may determine a megaloblastic form of anemia, but may also be associated with low platelet counts and peripheral neuropathy. Elevated levels of homocysteine, which constitute a risk factor for cardiovascular events, may be observed associated to reduction of levels of Vitamin B12.

Moreover, hypo/achloridia determines an increase in serum gastrin levels; this hormone stimulates the proliferation of enterochromafin-like cells (ECL), with a possible development of hyperplasia, which is in turn considered a precursor lesion of neuroendocrine tumors of the gastric mucosa (figure 1).

Vitamin B12 deficiency

Vitamin B12 (cobalamin) deficiency (9) may be associated with various cytological effects due to its key role as a cofactor within several metabolic pro-

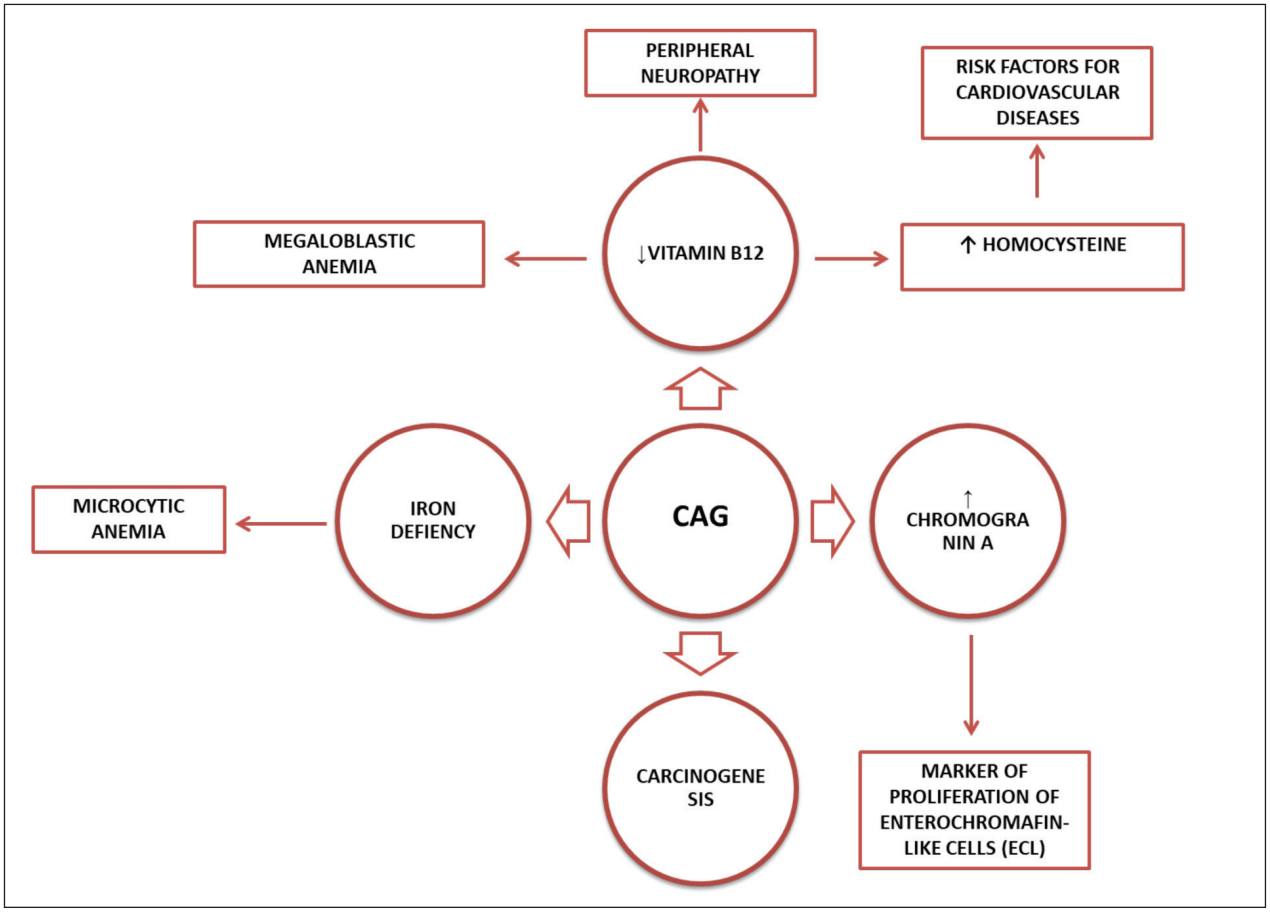

Figure 1. Clinical manifestations of chronic atrophic gastritis (CAG)

cesses, the most important of which implies the conversion of homocysteine in methionine by the enzyme homocysteine-methyltransferase, with a negative impact on the synthesis of nitrogenous compounds and consequently on DNA synthesis. This explains the repercussions of Vitamin B12 deficiency on hematopoiesis, with development of megaloblastic anemia (with mean corpuscular volume >90 fl), defined as pernicious anemia (antibodies against parietal cells of gastric mucosa, intrinsic factor, proton-pump, and or gastrin receptors).

As gastroenterological, neurological and hematological symptoms arise slowly and insidiously, patients frequently seek medical advice when the disease is already at an advanced stage. Anemia is often associated with tachycardia, vertigo, and dyspnea on exertion, while digestive manifestations of CAG may include post-prandial discomfort, diarrhea, and anorexia. Paleness of anemia is often combined with a very mild jaundice, the latter due to intramedullary hemolysis, resulting in a characteristic lemon-color complexion. Hunter's atrophic glossitis is also frequently encountered, with a dry, reddened, beefy and smooth tongue.

Another important consequence of Vitamin B12 deficiency is neuropathy; injury to the central nervous system has been found in nearly three fourths of all florid pernicious anemia patients, and may be present even in the absence of hematological alterations (10). Neurological alterations might constitute the cardinal and/or presenting clinical form (11). The spinal cord is mainly involved, with demyelination and atrophy, occasionally followed by axonal loss. These alterations lead to spastic paraparesis, sensory ataxia, visual disturbances, unsteady gait, and altered nervous reflexes. Cognitive disturbances may also be seen including memory loss, apathy, depression, and ultimately more complex behavioral changes. Sensory-motor peripheral polyneuropathy, or symmetric glove-and-stocking ("numb hands and feet syndrome") may present acutely, with tingling in the distal aspect of the toes, numbness, coldness, a pins-and-needles feeling, and occasional feelings of swelling or constriction (12).

Hematological alterations aside from macrocytic anemia may include hypersegmented polymorphonuclear neutrophils, increased platelet volume and thrombocytopenia. Serum levels of bilirubin, ferritin and lactate dehydrogenase may be elevated due to ineffective erythropoiesis (7).

Iron deficiency

Microcytic, hypochromic anemia, with all its clinical manifestations, frequently precedes the development of megaloblastic anemia in patients with CAG (13, 14). The pathophysiology of iron deficiency seems to be linked to four mechanisms: *(1)* chronic occult bleeding from gastric microerosions, *(2)* competition with *H. pylori* for dietary iron, *(3)* hypochlorhydria, and *(4)* upregulation of inflammatory hepcidin. Whether megaloblastic anemia or microcytic anemia develops seems to be dependent, at least in part, upon genetic factors. A genetic variant of transcobalamin II, related to lower Vitamin B12 levels, was more frequently associated with pernicious anemia in a cohort of patients with atrophic gastritis(15).

CAG has been reported in approximately 20-30% of cases of iron-deficiency anemia refractory to iron supplementation. Parietal cell atrophy and the ensuing hypochlorhydria negatively affect intestinal iron absorption. Moreover, up to 50% of patients with unexplained iron-deficiency anemia refractory to therapy has an active *H. pylori* infection. This association between *H. pylori* infection is further supported by the fact that eradication of the infection leads to resolution of anemia. In fact, according to several guidelines and the Maastricht V consensus on *H. pylori*, its eradication is advised in patients with iron deficiency anemia of unknown cause which is refractory to iron supplementation (16).

Hyperhomocysteinemia

Homocysteine, a sulphur-containing amino acid derived from methionine, is principally metabolized via methionine-synthase as the remethylation cycle, which is dependent on the presence of both Vitamin B12 and folate as co-factors. Elevated plasma homocysteine concentrations are now recognized as independent risk factors for cardiovascular diseases, and also seem to play an important role in the development of dementia, diabetes mellitus, and renal disease. By direct toxicity to endothelial cells and impairment

of endothelium-dependent vasodilation, hyperhomocysteinemia leads to progressive damage of the intima of the vascular wall.

Vitamin B12 and folate deficiencies constitute common causes of hyperhomocysteinemia, the former being a feature of chronic atrophic gastritis. Moreover, *H. pylori* infection per se, irrespective of atrophy of the gastric mucosa, has been associated with reduced plasmatic levels of Vitamin B12 and epidemiological studies have reported an association between *H. pylori* infection and coronary heart disease (17). Atrophic gastritis, rather than *H. pylor*i infection, is possibly a contributing factor to hyperhomocysteinemia, via Vitamin B12 malabsorption.(9)

Gastrointestinal symptoms

CAG has traditionally been considered silent from a gastrointestinal perspective. However, if sought, symptoms are usually present in a conspicuous portion of these patients. It has been reported that heartburn and regurgitation are present in approximately 24% and 12% of patients, respectively, while other frequent symptoms include postprandial fullness and early satiety in 7.1% and 10.1%, respectively (18). Another recent study showed that 56.7% of CAG patients presented one or more gastrointestinal symptoms; dyspepsia, subtype postprandial distress syndrome was the most frequent symptom, affecting more than half of symptomatic patients (4). A small, but interesting study in which 24 h multichannel intra-luminal impedance pH was performed in 41 patients with autoimmune CAG showed that acid reflux rarely occurred whereas increased non-acid reflux was found, and it correlated to symptoms in some patients. This group also observed that psychopathological profile plays a role in the occurrence of symptoms, and that the use of antisecretory drugs was generally inappropriate and clinically ineffective (19).

Postprandial related symptoms and epigastric pain syndrome (20) was significantly more prevalent in male patients with atrophy of the corpus and females with atrophy of the antrum, compared to patients with different topography of atrophy (20). Thus, authors conclude that the extent of atrophic gastritis appears to determine the predominant symptoms in a gender-dependent manner.

Coexisting autoimmune diseases

Autoimmune diseases tend to cluster, and autoimmune gastritis is more frequent in patients with autoimmune thyroid disease, vitiligo, and type 1 diabetes mellitus,. However, it is also true that anti-parietal cell antibodies, which are not specific for pernicious anemia and can be present in 7.8-19.5% of the general healthy adult population, are more prevalent in the serum of patients affected by these conditions, without necessarily having actual autoimmune gastritis (21). Prevalence of concomitant autoimmune diseases in patients with CAG has been reported to be as high as 40% (4), with the most frequent disorders being thyroid disease, vitiligo, alopecia, diabetes, hemolytic anemia, rheumatoid arthritis, psoriasis, autoimmune hepatitis, myasthenia gravis, and Sjögren's syndrome.

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