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Chronic autoimmune gastritis and its relation to megaloblastic anemia – Main histopathological and pathophysiological characteristics

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ABSTRACT
Chronic autoimmune gastritis is a sustained inflammation of the stomach, characterized by being immune-mediated against intrinsic factor-producing parietal cells, leading to nutritional deficiencies that can result in anemia. This study investigates the prevalence and underlying mechanism of anemia in patients with chronic autoimmune gastritis, focusing on iron deficiency anemia and megaloblastic vitamin B12 deficiency anemia. A literature review on the subject was carried out, in databases of scientific relevance and verified by peers, whose inclusion criteria allowed only relevant studies on the subject, published in the last five years, that establish a relationship with chronic autoimmune gastritis and anemia. Thus, the exclusion criterion left aside studies on chronic gastritis due to other etiologies, those cases not related to anemia, or other studies not relevant to the general objective. In the pathophysiological framework, there is an autoimmune destruction of gastric parietal cells, which leads to a reduction in the secretion of hydrochloric acid and intrinsic factor, essential for the absorption of vitamin B12 and iron, predisposing to iron deficiency and megaloblastic anemia. Histological examination reveals gastric atrophy with loss of glands, lymphocytic infiltration, and presence of plasma cells. Symptoms include dyspepsia, loss of appetite, and clinical signs of anemia such as pallor, fatigue, and, in severe cases, neurological symptoms of B12 deficiency. Chronic autoimmune gastritis should be considered as a significant underlying cause of anemia in patients with chronic gastrointestinal symptoms. Regular monitoring and proactive management of nutritional deficiencies in these patients is critically important to improve clinical outcomes and quality of life. Future research should explore therapeutic strategies to mitigate the progression of gastric atrophy and prevent the development of anemia in this specific population.

Keywords: Intrinsic actor, Inflammation, Atrophy, Vitamin B12.

1 INTRODUCTION

Chronic autoimmune gastritis, sometimes known as autoimmune atrophic gastritis, is an immune-mediated disorder that predominantly affects the stomach, leading to progressive morphological changes and eventual loss of functional gastric cells. This type of gastritis is characterized by a process of chronic inflammation, which results in atrophy of the gastric mucosa, specifically the parietal cells, with important clinical implications, including the malabsorption of iron and vitamin B12, as well as an increased risk of gastric carcinoma1.

Chronic autoimmune gastritis originates through an autoimmune response directed against the cellular components of the stomach. Anti-parietal cell and anti-intrinsic factor antibodies are typical findings in affected patients, contributing to cell destruction and eventual dysfunction. The loss of parietal cells decreases the production of hydrochloric acid, essential for nutrient absorption, and intrinsic factor, crucial for the absorption of vitamin B12. Cellular immunity also plays a critical role, through T lymphocytes, which eventually infiltrate the gastric mucosa and contribute to inflammation and tissue damage1.

It should be noted that chronic autoimmune gastritis is not the same pathology as chronic

atrophic gastritis. Although both types of gastritis involve gastric atrophy, their etiologies and clinical manifestations can differ significantly. Chronic atrophic gastritis generally refers to any form of gastritis that results in atrophy of the gastric mucosa, and can be caused by factors such as *Helicobacter pylori* infection, while chronic autoimmune gastritis is specifically an autoimmune disease1.

H. pylori-induced *chronic atrophic gastritis* is associated with active inflammation, while autoimmune gastritis tends to present milder inflammation with a marked increase in specific antibodies and more focused and severe atrophy. Anatomopathologically, chronic autoimmune gastritis shows a predominant atrophy in the body and gastric fundus, with relative preservation of the antrum. This distribution of atrophy opposes the view in *H. pylori-related* atrophic gastritis, which commonly affects the antrum. Microscopic findings include loss of parietal and major cells, lymphocytic infiltration of the lamina propria, and the presence of intestinal metaplasia and neuroendocrine cells, which are adaptations to chronic acid depletion1.

This study aims to broaden the understanding of chronic autoimmune gastritis, delineating its inflammatory mechanisms, differentiating it from other forms of atrophic gastritis, establishing its correlations with the development of anemia, and highlighting its distinctive anatomopathological characteristics to improve diagnostic and management strategies [1].

2 MATERIALS AND METHODS

A comprehensive literature search was conducted using medical databases such as PubMed, SciELO, Elsevier, Google Scholar, and other relevant sources. Specific search terms, such as 'anaemia', 'chronic gastritis', 'pathophysiology' and 'autoimmune', were used to collect relevant studies.

Inclusion criteria were applied to select studies related to autoimmunity, pathophysiology, pathological anatomy and semiology of chronic autoimmune gastritis. Likewise, we sought to include all types of studies that related chronic gastritis with the development of anemia. We excluded studies that did not directly address these aspects, lacked methodological rigor, or excluded anemia among their writing criteria.

Original articles, systematic reviews, and meta-analyses were selected that provided a comprehensive view of the various aspects of chronic autoimmune gastritis. Priority was given to recent publications and publications under 5 years of age, but classic repaginated studies were also included, to contextualize the evolution of knowledge on the subject.

Relevant data were extracted from the selected studies, including information on the

different etiopathogenesis for the disease, pathological findings, advances in pathophysiological understanding, and clinical presentation. Differences in methodologies and results were recorded for comparative analyses. A narrative synthesis of the findings was performed to provide an overview of current research on chronic autoimmune gastritis. Emerging patterns, discrepancies in results, and areas for future research were highlighted. This approach allowed for the construction of a coherent narrative.

A critical evaluation of the methodological quality of the included studies was carried out. We took into account study design, sample size, representativeness of the population, and validity of conclusions to ensure the reliability of the review.

3 THEORETICAL FRAMEWORK

Chronic gastritis can be defined as a chronic and persistent inflammation of the gastric mucosa, with multiple etiologies and pathological manifestations. That said, we can classify chronic gastritis based on its pathogenic causes and histological features, such as chronic autoimmune gastritis, the subject of this study, and gastritis induced by other factors, such as *Helicobacter pylori infection.* This disorder has been recognized for several centuries, although its detailed understanding has evolved significantly with advances in gastroenterology, immunohistochemistry techniques, and scientific research2.

Historically, the symptoms associated with gastritis, whether chronic or acute, have been described since ancient times, but it was not until the nineteenth century that the pathological characteristics of the disease began to be identified. Gastritis as an inflammatory process of the stomach was initially documented by the German physician Georg Ernst Stahl in the eighteenth century, although the most precise and systematic descriptions came with advances in biopsy techniques in the twentieth century2,3.

The discovery and subsequent taxonomic classification of *Helicobacter pylori* in 1982 by Barry Marshall and Robin Warren, revolutionized the understanding of chronic gastritis, establishing a clear infectious cause for many of its forms and transforming its treatment therapy, as well as opening the doors for a better understanding of prevention and recovery care measures2, Question 3.4.

Initially, gastritis was mainly described by clinical symptoms such as abdominal pain and dyspepsia. With the advent of diagnostic and imaging techniques, such as endoscopy, as well as with the improvement of histological techniques, the definition of gastritis has been refined towards an approach based on anatomopathological findings3,4.

Chronic gastritis, in particular, has been categorized into subtypes based on inflammation pattern, etiology, and histological features, with chronic autoimmune gastritis and chronic atrophic gastritis being the primary forms. The former is characterized by the presence of antibodies against parietal cells and intrinsic factor, and the latter is mainly related to chronic *H. pylori infections*, although other etiologies due to microorganisms are not ruled out4,5,6.

Chronic gastritis is now recognized as a precursor to numerous gastrointestinal complications, including gastric atrophy, intestinal metaplasia, and in more severe cases, gastric adenocarcinoma. Arguably, the most underestimated chronic complication, which is why it is often undiagnosed, is pernicious anemia4,5,6,7.

Anemia is defined as any condition in which there is a deficiency in the quantity or quality of red blood cells in the blood, resulting in a reduced ability of the blood to carry oxygen. This disorder can be caused by multiple factors, including nutritional deficiencies, blood loss, destruction of red blood cells, or inadequate production of red blood cells. The most common symptoms include fatigue, paleness, shortness of breath and, in severe cases, heart problems6,7.

Pernicious anemia, the most common form of megaloblastic anemia, is primarily caused by deficiency of vitamin B12, which is essential for the formation of DNA in dividing cells, including the precursors of red blood cells in the bone marrow. This deficiency is due, in most cases, to inadequate absorption of vitamin B12, due to a lack of intrinsic factor, a protein produced by the parietal cells of the stomach that is crucial for the absorption of vitamin B12 in the intestine7,8,9.

Pernicious anemia can also be considered an autoimmune disease, as the immune system attacks and destroys gastric parietal cells, leading to a critical reduction in the production of intrinsic factor. Without sufficient intrinsic factor, vitamin B12 cannot be absorbed effectively, resulting in its deficiency and subsequent development of megaloblastic anemia6,7,8.

Typically, the signs and symptoms of pernicious anemia go beyond the typical signs of anemia and include neurological symptoms such as numbness and tingling in the hands and feet, coordination problems, and, in severe cases, cognitive changes due to nerve involvement. Early detection and treatment are crucial to prevent permanent complications7,8.

On the other hand, megaloblastic anemia is characterized by the presence of megaloblasts, which are abnormally large erythroid precursors in the bone marrow, resulting from defective nuclear maturation due to disturbances in DNA synthesis. While vitamin B12 deficiency is a common cause, folic acid deficiency can also result in megaloblastic anemia. Not all types of megaloblastic anemia are considered pernicious anemia, but pernicious anemia is the most

common etiology for megaloblastic anemia7,8,9,10.

The diagnosis of pernicious anemia and megaloblastic anemia is made through blood tests that show not only low hemoglobin levels and alterations in the size and shape of red blood cells, but also specific tests such as vitamin B12 levels, intrinsic antibody tests, and acid levels folic8,9,10. From a pathophysiological point of view, chronic autoimmune gastritis is a disease characterized by a progressive destruction of the parietal cells of the stomach by autoimmune mechanisms. This pathological process results in profound alterations in gastric structure and function, with important clinical consequences[9,10,11].

The etiopathogenesis of chronic autoimmune gastritis involves an immune response directed against gastric parietal cells and intrinsic factor. Specific mechanisms include the formation of autoimmune antibodies that attack cellular components, including the hydrogen and potassium ion channel ATPase (proton pump), as well as intrinsic factor. This autoimmune response leads to a pattern of chronic phase inflammation that eventually results in atrophy of the gastric mucosa, especially in the glands of the body and the back of the stomach9,10,11.

The loss of parietal cells compromises the secretion of gastric acid, leading to a state of hypochlorhydria or achlorhydria. Decreased gastric acidity negatively affects the absorption of essential nutrients, such as iron and vitamin B12, and disrupts the acid barrier that protects against infections by enteric pathogens. In addition, intrinsic factor deficiency prevents normal absorption of vitamin B12, which can lead to pernicious anemia, a serious complication of chronic autoimmune gastritis10,11,12.

Unlike chronic autoimmune gastritis, *Helicobacter pylori-induced* gastritis typically begins in the anthropopylorus, so much so that the microorganism was named for this fact, and is associated with active inflammation rather than initial significant atrophy. H. *pylori infection* stimulates the production of inflammatory cytokines and other mediators that promote the infiltration of inflammatory cells into the gastric mucosa11,12.

Although both conditions can lead to gastric atrophy and increased risk of gastric cancer, *H. pylori* gastritis is more likely to have an active inflammatory phase before developing atrophy. In addition, the pathology in *H. pylori* gastritis is mainly mediated by the host's response to chronic bacterial infection, unlike the autoimmune mechanisms in chronic autoimmune gastritis12,13,14.

From an anatomopathological point of view, chronic autoimmune gastritis manifests itself with characteristic changes in the gastric mucosa, both at the macroscopic and microscopic levels. These changes are essential for diagnosis and understanding of disease progression.

Chronic autoimmune gastritis typically affects the body and the bottom of the stomach, although in advanced cases it may involve the entire stomach13,14.

Macroscopically, the stomach may appear pale and thin with a noticeable reduction in the thickness of the gastric wall. The affected areas show a smooth surface, with loss of normal roughness, reflecting the underlying atrophy of the mucosa. In severe cases, this thinning and loss of normal structure can confer an almost translucent appearance to the gastric wall [14,15].

Microscopic findings are essential to confirm the diagnosis of chronic autoimmune gastritis, the distinguishing feature being the progressive atrophy of the gastric glands, especially in the areas of the body and fundus. This atrophy is characterized by the loss of normal glands and their replacement by fibrous tissue or intestinal glands (intestinal metaplasia)[15,16,17].

Although inflammation may not be as prominent as in other types of gastritis, a chronic infiltrate is typically seen in the lamina propria, composed primarily of lymphocytes and plasma cells. These infiltrates can form lymphoid aggregates or even follicles with germinal centers15,16,17.

Autoimmune destruction of parietal cells is a key finding. These cells are responsible for the secretion of acid and intrinsic factor, essential for the absorption of vitamin B12. In response to low gastric acidity, there may be compensatory hyperplasia of endocrine G cells, which secrete gastrin. This hyperplasia is commonly observed in the mucosa of the antrum16,17.

In contrast to chronic autoimmune gastritis, chronic *H. pylori* gastritis typically shows more active and aggressive inflammation, with neutrophilia and possible erosions, or even ulcerations. In addition, while H. *pylori* gastritis most frequently begins in the antrum and can spread to the body, autoimmune gastritis begins in the body and spreads to the antrum, but only in later stages16,17.

It can be concluded that among the most relevant microscopic findings for chronic autoimmune gastritis are the presence of plasma cells, lymphocytes, and occasional lymphoid follicles, with or without a germination center. Occasionally, we can also find the presence of eosinophils and neutrophils, but this finding is rare. There may be reduced cytoplasmic mucin and reactive epithelial changes, such as nuclear and nucleolar enlargement16,17.

Also, we can find subnuclear vacuolization in antral glands or pits, negatively stained with PAS, which probably represents a degenerative response to a cellular lesion found. Occasionally, there is intestinal metaplasia, which affects the mucosa of the anthropologist, as well as the body and fundus, with partial replacement by metaplastic goblet cells of intestinal morphology, absorbent cells and Paneth cells; This finding can be considered extensive if it

affects 25% of the biopsy tissue15,16,17.

In relation to intestinal metaplasia, it can be complete or incomplete. In the first, the mucosal pattern resembles the epithelium of the small intestine with goblet and absorbent cells, villi and crypts; Sialomucines predominate. In the second, there are no absorbent cells, the columnar cells resemble gastric foveolar cells; Neutral mucins and sulfomucins are present[15,16,17].

From a semiological point of view, we find that chronic autoimmune gastritis can manifest with a variety of gastrointestinal and systemic symptoms, with pernicious anemia being one of the most significant and potentially debilitating complications associated. The semiology of chronic autoimmune gastritis can be quite varied, reflecting the degree of gastric atrophy and the extent of autoimmune damage15,16,17,18.

Gastrointestinal signs and symptoms include dyspepsia, epigastric pain, nausea, early satiability, loss of appetite, among others. The symptoms may be accompanied by fatigue, generalized weakness and weight loss. Pernicious anemia is a direct complication of chronic autoimmune gastritis due to the lack of intrinsic factor, necessary for the absorption of vitamin B1217,20.

Among the main hematological complications we can describe, mainly, extreme fatigue, muscle weakness, dizziness, dyspnea, brief alteration of consciousness, among others. At the same time, among the long-term neurological manifestations, it is common to observe cases of peripheral neuropathy with alterations in gait, changes in cognitive perception, memory loss, transient alterations in the state of consciousness, among others17,18,20,21.

The diagnosis of chronic autoimmune gastritis, as well as its intrinsic relationship with pernicious anemia, is made by correlating the clinical findings observed by the health professional, together with laboratory studies and endoscopic results. Low serum levels of vitamin B12, the presence of antibodies against intrinsic factor and anti-parietal cell antibodies, in correlation with endoscopic findings of marked atrophy of the gastric mucosa, mainly at the glandular level, as well as anatomopathological results, will confirm the diagnosis of this pathology [17,18,19,20].

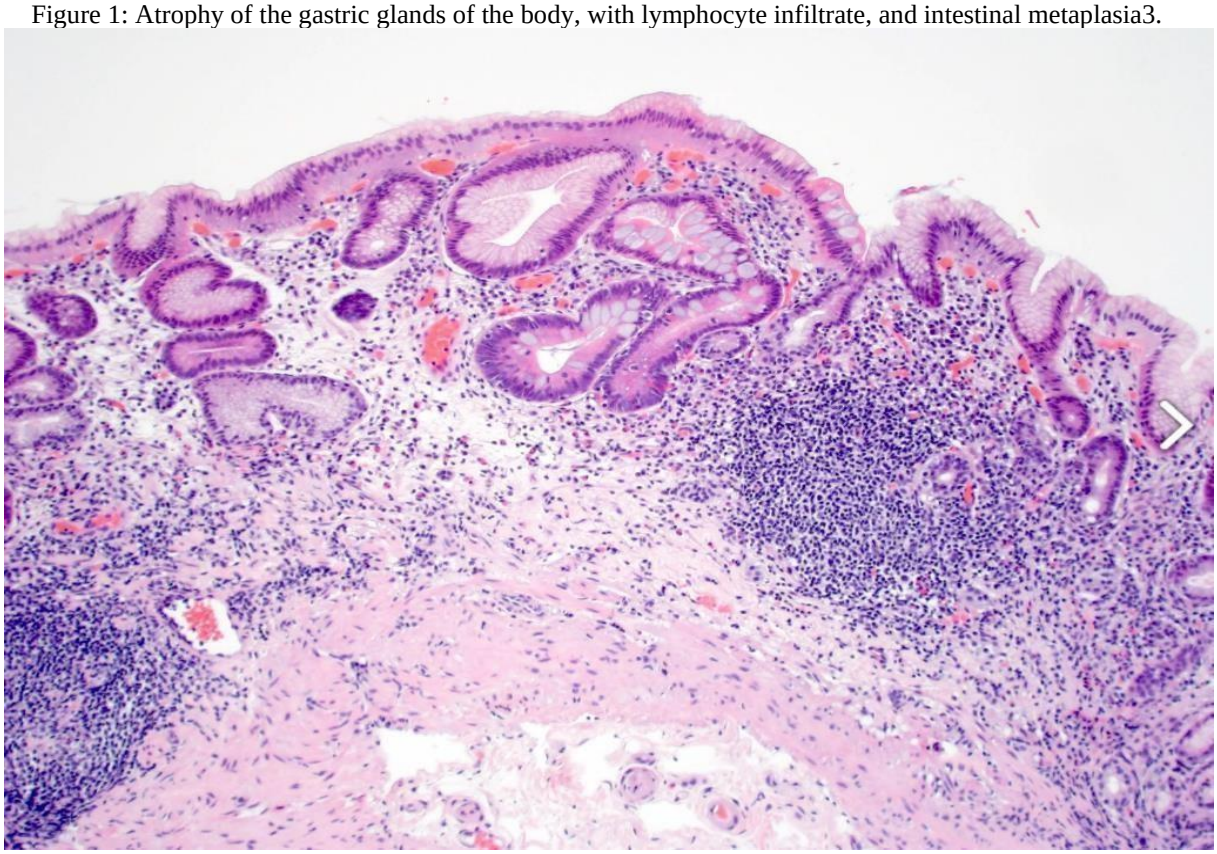
As previously mentioned, the main differential diagnosis for chronic autoimmune gastritis is chronic gastritis induced by H. pylori. Atrophy occurs at different levels of the gastric mucosa, as well as the level of chronic phase inflammatory infiltrate differs between the two [18,19,20,21].

4 RESULTS AND DISCUSSION

Chronic autoimmune gastritis is a condition in which the mucosa of the gastric lining undergoes a chronic inflammatory process, whose etiopathogenesis lies in a mechanism of autoimmune injury, meaning that the presence of antibodies that attack the cells of the body itself can be verified. This inflammatory process, inevitably due to its chronicity, ends up generating an atrophy of the epithelial lining of the gastric mucosa – giving rise to an almost total destruction of parietal cells, which produce intrinsic factor and, finally, to the development of megaloblastic anemia[3,4,6,9,10].

From an anatomopathological perspective, chronic autoimmune gastritis presents with an atrophy of the gastric mucosa, in this case, much more prominent in the body and in the gastric fundus. This atrophy leads to considerable destruction of parietal cells, which ends up leading to achlorhydria and intrinsic factor deficiency, with a less visible pattern of inflammation, but with the presence of specific autoantibodies7,9,12,14.

Figure 1: Atrophy of the gastric glands of the body, with lymphocyte infiltrate, and intestinal metaplasia3.



Clinically, it is correct to state that chronic autoimmune gastritis may be an important precursor to other types of more severe gastric pathologies, such as gastric cancer. Chronic autoimmune gastritis carries an increased risk of gastric carcinoma of the intestinal type, but not of the diffuse type, this is due to deep atrophy and gastric metaplasia. Finally, it should be noted

that among the most severe specific complications is pernicious anemia due to the malabsorption of B12[15,18,19].

In terms of treatment, the management of chronic autoimmune gastritis focuses on the treatment of vitamin B12 deficiency as well as the control of autoimmunity. That said, chronic gastritis of autoimmune origin does not present a clear curative approach to date, unlike chronic gastritis of pathogenic origin due to *H. pylori* infection; therefore, for these patients, it is only possible to offer a treatment-focused approach14,18,20.

5 FINAL CONSIDERATIONS

The present bibliographic review focused on chronic autoimmune gastritis, as well as its relationship with megaloblastic anemia, has presented us with a stratified and multifactorial vision, where pathophysiology, pathological anatomy and clinical semiology can be combined, in order to offer a broader panorama in relation to the subjects affected by this pathology. At the conclusion of this literature review, some specific research considerations are highlighted, which help us to delimit the current challenges related to treatment, as well as future research directions related to this autoimmune condition.

Chronic autoimmune gastritis is a progressive and insidious disease, which predominantly affects the body and gastric fundus, resulting in inevitable atrophy of the gastric lining mucosa, along with dysfunction of parietal cells. This autoimmune condition is significantly associated with the development of megaloblastic anemia, due to the loss of gastric ability to synthesize intrinsic factor, a glycoprotein made by parietal cells, essential for the absorption of vitamin B12. Throughout this article, it has been highlighted that megaloblastic anemia is not only a complication of chronic autoimmune gastritis, but also a significant indicator of disease progression and a predictor of other possible more serious complications, including neurological alterations and an increased risk of gastric carcinoma. Therefore, early recognition and therapeutic intervention are of paramount importance to prevent the progression of anemia and mitigate other risks associated with this condition.

The treatment of chronic autoimmune gastritis and megaloblastic anemia entails a number of challenges, mainly due to the autoimmune nature of the disease – so the manifestation of the clinical manifestation in these patients is silent, insidious and, on many occasions, unnoticed by health professionals.

Currently, the administration of vitamin B12 by injection is the standard treatment for anemia, since there is still no cure for the underlying gastric atrophy. This underscores the need for future research geared toward developing therapeutic strategies that can modify the autoimmune response or even reverse gastric atrophy. Finally, it is possible to conclude that chronic autoimmune gastritis represents a complex and multifaceted challenge in the field of gastroenterological medicine, since it requires a multidisciplinary approach for its appropriate treatment.

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