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Review

CURRENT UNDERSTANDING OF ATROPHIC GASTRITIS AND INTESTINAL METAPLASIA AS A PREMALIGNANT LESION OF GASTRIC CANCER

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Summary

Gastric cancer is the fifth most common and third leading cause of cancer death worldwide. Patients with chronic atrophic gastritis (CAG) and intestinal metaplasia (IM) are at increased risk of developing gastric cancer (GC). It is common for CAG to precede IM, but the etiology of the two conditions is not always the same. Different scoring systems are used to assess HAG, MI, and GC risk, making it difficult to interpret results from investigations and management of these conditions.

Keywords: chronic atrophic gastritis, intestinal metaplasia, gastric precancerous lesion

Background

Chronic atrophic gastritis and intestinal metaplasia are considered precancerous conditions as they represent the background against which dysplasia and gastric adenocarcinoma may develop [1]. According to Correa's 1975 model, chronic inflammation of the gastric mucosa triggers a series of changes that progress through chronic gastritis, multifocal atrophic gastritis (MAG), and intestinal metaplasia [2].

In the updated 1992 model, according to Lauren's classification, the interstitial type of cancer is the final stage in the development of the following cascade: non-atrophic chronic gastritis, multifocal atrophic gastritis, interstitial metaplasia (of the complete and incomplete type), dysplasia (low-grade and high-grade), and invasive intraepithelial adenocarcinoma [3, 4].

The division of gastritis into non-atrophic and atrophic is essential in determining the risk of developing gastric carcinoma. Furthermore, patients with severe atrophy and extensive metaplasia are at increased risk of GC [5]. Over the years, various systems for classification have been used. However, atrophic gastritis is still a

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histopathological diagnosis that is difficult to make.

This review summarizes the data on the current understanding of atrophic gastritis and intestinal metaplasia as precancerous gastric lesions.

Methods

An electronic search was performed in the PubMed database from 2012 to 2022, using the keywords "chronic atrophic gastritis," "intestinal metaplasia," and "precancerous gastric lesions." Inclusion criteria were full-text meta-analyses or systematic reviews written in English and patients studied with histologically verified CAG or IM. The criteria applied were met by 52 studies.

Discussion

The first morphologic classification of gastritides was that of Schindler and Henning in 1947, based on histologic material collected at random during surgical procedures of the stomach [6]. According to this classification, gastritis can be superficial, atrophic, and hypertrophic. Individual cases of these take different courses with different prognoses. However, it is noted that superficial gastritis can progress to become atrophic with time. Later, in 1972, Whitehead, Truelove, and Gear proposed a new classification that linked the topography of gastritis to activity [7]. "Activity" implied the presence of an active inflammatory infiltrate of mononuclear cells against the background of degenerative epithelial changes and polymorphonuclear infiltrates. The disadvantage of this classification is that it was not relevant to the etiology and pathogenesis of gastritis and did not include its specific forms.

In 1973, Strickland and Mackay proposed the existence of two distinct forms of gastritis based on the presence or absence of anti-parietal antibodies (APA) and damage to the antral mucosa [8]. According to these criteria, type A gastritis develops as diffuse corpus gastritis without damage to the antral mucosa, the presence of positive APA, severe disturbance of gastric secretion, and impaired absorption of vitamin B12. Type B causes focal atrophy in the antrum and body, APAs are negative, gastric secretion is mildly impaired, and vitamin B12 absorption is rarely disturbed. Type A is thought to be of autoimmune origin due to the presence of APAs, while type B is due to external environmental factors that were later identified as infection with H. pylori [9]. In 1990, the first Sydney classification of gastritis was published. This original version was much criticized, especially its morphological section, where concepts such as diffuse antral gastritis and multifocal atrophic gastritis had been dropped. Subsequently, an updated version of the Sydney classification was adopted in Houston in 1994 and published in 1996 by Correa, Dixon et al. [10]. It established a general morphological concept for two different forms of chronic atrophic gastritis. Additional biopsies from the angular notch of the stomach were added, and a visual analog scale for grading the histological changes in the mucosa. According to the updated classification, it is recommended that five biopsies be taken in separate vials for different areas of the stomach: a) from the antrum - one sample from the lesser curvature and one sample from the greater curvature, both at a distance of 2 to 3 cm from the pylorus; b) one sample from the angular notch; and c) from the body - one sample from the lesser curvature taken proximally at about 4 cm from the angular notch and one sample from the middle portion of the greater curvature, approximately 8 cm from the cardia [10]. The updated Sydney classification is the most widely used, but it does not predict the risk of developing gastric cancer in patients with CAG.

In 2007, an international group of expert gastroenterologists and pathologists created a new gastritis assessment system called OLGA (the Operative Link for Gastritis Assessment) [11]. This system considered the degree of mucosal atrophy and related it to its location in the stomach, resulting in a progressively increasing risk of developing GC. The biopsy protocol and staging of atrophy were applied according to the updated Sydney classification. In each biopsy specimen, atrophy is scored on a four-point scale from 0 to 4 (0 - no atrophy, 1- mild atrophy, 2- moderate atrophy, 3- severe atrophy). The final score is formed by adding the stages of atrophy in specimens from the antrum and corpus. According to the OLGA system, patients in

an OLGA stage 0 and OLGA stage I have the lowest risk. In contrast, patients in the advanced stage (OLGA III and OLGA IV) are at high risk of developing GC and should be followed up endoscopically. For proper interpretation of OLGA results, good communication between pathologists and gastroenterologists is crucial.

Due to the differences in interpreting the term "atrophy," OLGA was later modified as OLGIM (the Operative Link for Intestinal Metaplasia) [12]. The biopsy and staging protocols were retained, but intestinal metaplasia was assessed instead of atrophy. This system for assessing the risk of GC is considered to have a better level of agreement among pathologists.

Despite the advent of new classifications, defining the terms they use remains debatable. The commonly used definition of "atrophy" is "loss of glands" [13]. In order to increase agreement between the different schools of pathology, this was changed to 'loss of corresponding glands." [14]. This loss may occur following prolonged inflammation of the glands and may result in various phenotypes of atrophic transformation. Replacement of the affected tissue with fibrosis tissue may occur, which does not imply a change in the corresponding epithelial tissue type. However, a metaplastic transformation of the atrophied glands with another cell type not characteristic of gastric structures (metaplasia) may also occur. According to a WHO definition (2019), any metaplastic transformation in the glands is classified as metaplastic atrophy [15]. In the stomach, a metaplastic transformation can lead to intestinal or pseudopyloric (spasmolytic polypeptide expressing) metaplasia. The role of pseudopyloric metaplasia concerning gastric cancer is controversial: it may undergo intestinalization.

On the other hand, many studies have confirmed the role of intestinal metaplasia in the development of intestinal adenocarcinoma. Histological classifications of IM have been established. These allow stratification of patients according to the risk of GC. As early as 1979, Jass and Filipe described several types of IM, depending on the type of secreting mucins: type I (complete or small-intestinal type) with enterocytes with microvilli, sialomucin-producing cup-shaped cells, and Paneth cells; incomplete type II and type III (of cup-shaped cells with large vacuoles, without enterocytes), producing gastric and intestinal mucins, and type 3 cells that produce sulfomucins [16]. Currently, the subtyping of IM into complete (type I or small intestinal type) and incomplete (type II and III, or large intestinal type) is widely used, which is similar to the classification of Jass and Filipe.

Concerning CAG and the risk of GC, Correa has stated that it is appropriate to divide chronic gastritis into antral dominant, corpus dominant, and multifocal, which is related to precancerous lesions.

Antral dominant chronic gastritis is relatively rare. In such patients, metaplastic changes result from a past or present Helicobacter pylori infection. Atrophy, limited to the distal mucin-secreting mucosa with inflammatory changes and normal to mildly inflamed corpus mucosa without atrophic changes, is common [17]. The relationship between antral and multifocal gastritis is debatable. Some authors have suggested that the atrophy confined to the antrum precedes multifocal atrophy, and the two actually represent different stages of the same disease. This hypothesis has not been proven yet.

Corpus dominant gastritis is another subtype. A different type of atrophy is seen in the fundic glands, pathognomonic of an autoimmune etiology and with an increased risk for cancer. The so-called type A or autoimmune gastritis is characterized by severe diffuse atrophy occupying the fundus, hypochlorhydria, hypergastrinemia, pernicious anemia, and normal antral mucosa. Autoimmune aggression results from circulating antibodies against parietal cells and is an intrinsic factor in the serum, gastric juice, and plasma cells. Rarely, autoimmune atrophy is combined with antral atrophy due to H. pylori infection. Whether these are distinct pathogenetic mechanisms in developing topographically separate forms of gastritis or the infection has a triggering effect on the autoimmune disease is still unclear [18]. Patients with autoimmune gastritis may also have other immune-mediated diseases such as Hashimoto's thyroiditis, insulin resistance, vitiligo, and psoriasis. According to Correa, autoimmune gastritis is not part of the precancerous cascade, although such patients are at increased risk for adenocarcinoma and neuroendocrine tumors [19, 20].

Multifocal atrophic gastritis is the first step in the precancerous cascade [21]. The atrophic areas with metaplastic glands are anatomical structures prone to phenotypic and genotypic changes leading to cancer [22]. The risk of gastric cancer rises in a proportion equal to the degree of atrophic changes, with atrophic pangastritis considered the most significant risk. Different cell types - neutrophils, monocytes, macrophages, mast cells, dendritic cells, and lymphocytes, are associated with chronic inflammation in the altered tissues [23]. Inflammatory cells in the atrophic mucosa produce various cytokines and reactive oxygen species that lead to damage of cellular DNA through reactions such as oxidation, nitration, nitrosation, and halogenation. These reactions unlock the multi-step process of carcinogenesis by damaging the cellular components and increasing the number of mutations.

In one of the first meta-analyses on the relationship between HAG and GC, Spence et al. published data from five studies in Europe and three in Asia. According to these results, the risk of developing GC in patients with HAG ranged between 0.1 and 0.5%. The stage and severity of gastritis were also important: patients with severe atrophy and advanced dissemination were at a higher risk [20]. According to data published so far, the prevalence of HAG ranges between 0 and 10.9% a year [24]. The difference in the data is attributed to the fact that different methods are used to diagnose CAG. Some studies use endoscopic methods with histological verification, while others rely on serological markers. In addition, different etiological causes may lead to mucosal atrophy. On the one hand, an autoimmune reaction with targeted anti-parietal antibodies (APA) can lead to loss of the own glands; on the other hand, prolonged infection with Helicobacter pylori, a class 1 carcinogen, can also be the cause of transformation of the gastric epithelium [5]. According to P. Correa, the development of multifocal atrophic gastritis associated with H. pylori underlies the cascade of precancerous lesions [3]. This assumption has been supported by data obtained from a large meta-analysis on the benefits for healthy individuals from Helicobacter eradication and the associated reduced morbidity and mortality due to gastric cancer [24]. Uemura et al. published data from a prospective study on 1526 individuals, 1246 of them infected with H. pylori. During the follow-up period (7.8 years on average), 36 individuals developed GC, all positive for H. pylori [25]. In another cohort study, Ohata et al. examined in consequence the rise in the risk of GC in several groups. The group without atrophic gastritis positive subjects was found with the lowest risk for GP (H. pylori (+)/CAG(-)), followed by H. pylori (-)/CAG(+) without metaplasia [26]. The group with severe atrophy, IM, and negative for Helicobacter pylori(-)/CAG(+) had the highest risk. Patients positive for H. pylori and IM had a 6.4-fold increased risk for GC than those infected with H. pylori without IM [27]. These findings explain why IM is referred to as a "point of no return" in some studies: the genetic changes in gastric stem cells are thought to be irreversible. In such cases, it is believed that eradicating H. pylori will not reduce the risk of GC. Depending on risk factors and family history of GC, strict protocols for endoscopic re-examination should be applied in these patients.

Conclusions

Different scoring systems are used for assessment of HAG and IM. However, histopathological diagnosis of atrophic gastritis is still a challenge. Introducing universally validated scales and methods into routine practice would contribute to the early detection and appropriate management of precancerous gastric lesions. In addition, good communication between gastroenterologists and pathologists is crucial for the proper management of HAG and IM.

References

1. Tsukuma H, Oshima A, Narahara H, Morii T. Natural history of early gastric cancer: a non-concurrent, long term, follow up study. Gut. 2000 Nov 1;47(5):618–21.
2. Correa P, Haenszel W, Cuello C, Tannenbaum S, Archer M. A model for Gastric Cancer Epidemiology. The Lancet. 1975;306(7924):58–60.
3. Correa P, Piazuelo MB. The gastric precancerous cascade. J Dig Dis. 2012;13(1):2–9.
4. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called

intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31–49.
5. Huang YK, Yu JC, Kang WM, Ma ZQ, Ye X, Tian SB, et al. Significance of serum pepsinogens as a biomarker for gastric cancer and atrophic gastritis screening: a systematic review and meta-analysis. PloS One. 2015 Nov 10;10(11):e0142080.
6. Schindler R. Chronic gastritis. Bulletin of the New York Academy of Medicine. 1939 May;15(5):322
7. Whitehead R, Truelove SC, Gear MW. The histological diagnosis of chronic gastritis in fibreoptic gastroscope biopsy specimens. J Clin Pathol. 1972;25(1):1–11.
8. Strickland RG, Mackay IR. A reappraisal of the nature and significance of chronic atrophic gastritis. Am J Dig Dis. 1973;18(5):426–40.
9. Graham DY. Helicobacter pylori infection in the pathogenesis of duodenal ulcer and gastric cancer: A model. Gastroenterology. 1997;113(6):1983–91.
10. Dixon MF, Genta RM, Yardley JH, Correa P, Batts KP, Dahms BB, et al. Classification and grading of Gastritis: The updated Sydney system. Am J Surg Pathol. 1996 Oct;20(10):1161–81.
11. Rugge M, Meggio A, Pennelli G, Piscioli F, Giacomelli L, De Pretis G, et al. Gastritis staging in clinical practice: The OLGA staging system. Gut. 2007;56(5):631–6.
12. Isajevs S, Liepniece-Karele I, Janciauskas D, Moisejevs G, Putnins V, Funka K, et al. Gastritis staging: Interobserver agreement by applying OLGA and OLGIM systems. Virchows Arch. 2014;464(4):403–7.
13. Andrew A, Wyatt JI, Dixon MF. Observer variation in the assessment of chronic gastritis according to the Sydney system. Histopathology. 1994;25(4).
14. Rugge M, Correa P, Dixon MF, Fiocca R, Hattori T, Lechago J, et al. Gastric mucosal atrophy: Interobserver consistency using new criteria for classification and grading. Aliment Pharmacol Ther. 2002;16(7):1249–59.
15. Gonzalez RS, Raza A, Propst R, Adeyi O, Bateman J, Sopha SC, et al. Recent advances in digestive tract tumors: updates from the 5th edition of the World Health Organization “Blue Book.” Archives of Pathology and Laboratory Medicine. 2021;145(5): 607–626
16. Jass JR, Filipe MI. A variant of intestinal metaplasia associated with gastric carcinoma: a histochemical study. Histopathology. 1979;3(3).
17. Rugge M, Genta RM. Staging and grading of chronic gastritis. Human Pathology 2005;36(3):228–33.
18. Coati I, Fassan M, Farinati F, Graham DY, Genta RM, Rugge M. Autoimmune gastritis: Pathologist’s viewpoint. World J Gastroenterol. 2015;21(42):12179–89.
19. Lenti MV, Rugge M, Lahner E, Miceli E, Toh BH, Genta RM, et al. Autoimmune gastritis. Nat Rev Dis Prim. 2020;6(1).
20. Correa P, Piazuelo MB. The gastric precancerous cascade. J Dig Dis. 2012;13(1):2–9.
21. Correa P. Human Gastric Carcinogenesis: A Multistep and Multifactorial Process- First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res. 1992;52(24):6735–40.
22. Graham TA, McDonald SA, Wright NA. Field cancerization in the GI tract. Future Oncol.2021;7(8): 981–993.
23. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? The Lancet. 2001 Feb 17;357(9255):539-45.
24. Adamu MA, Weck MN, Rothenbacher D, Brenner H. Incidence and risk factors for the development of chronic atrophic gastritis: Five year follow-up of a population-based cohort study. Int J Cancer. 2011;128(7):1652–8.
25. Ford AC, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer: Systematic review and meta-analysis. Gut. 2020;69(12):2113–21.
26. Uemura N. H. pylori infection and the development of gastric cancer in Japan. Nihon rinsho.2003;61(1):25–9.
27. Ohata H, Kitauchi S, Yoshimura N, Mugitani K, Iwane M, Nakamura H, et al. Progression of chronic atrophic gastritis associated with Helicobacter pylori infection increases risk of gastric cancer. Int J Cancer. 2004;109(1).