World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i13.1690

World J Gastroenterol 2011 April 7; 17(13): 1690-1693
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

How to assess the severity of atrophic gastritis

Yan-Cheng Dai, Zhi-Peng Tang, Ya-Li Zhang

Yan-Cheng Dai, Zhi-Peng Tang, Ya-Li Zhang, Department of Gastroenterology, Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 200032, China
Yan-Cheng Dai, Zhi-Peng Tang, Ya-Li Zhang, The Institute of Digestive Disease Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 200032, China
Author contributions: Dai YC, Tang ZP and Zhang YL contributed equally to this paper.
Supported by the Shanghai Leading Academic Discipline Project, No. J50305
Correspondence to: Zhi-Peng Tang, MD, Department of Gastroenterology, Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, 725 South Wanpin Road, Shanghai 200032, China. zhipengtang@sohu.com
Telephone: +86-21-64385700 Fax: +86-21-64392310
Received: September 16, 2010 Revised: December 1, 2010
Accepted: December 8, 2010
Published online: April 7, 2011

Abstract

Atrophic gastritis, is the main consequence of long-standing *Helicobacter pylori* infection, and is linked to the development of gastric cancer. The severity of atrophic gastritis is related to the lifetime risk of gastric cancer development, especially in terms of its degree and extent of mucosal damage. Therefore, it is important for clinicians to assess the severity of atrophic gastritis, interfere with the disease progress, and reverse gastric mucosal atrophy. In the article, we demonstrated some methods (conventional endoscopy, modern endoscopic technology and noninvasive methods) that may help assess the severity of atrophic gastritis and select the reasonable treatment protocols.

Key words: Atrophic gastritis; Endoscopy; Pepsinogen

Peer reviewer: Gerardo Nardone, MD, Professor, Department of Clinical and Internal Medicine, Gastroenterology Unit, Via Pansini 5 Napoli80131, Italy

Dai YC, Tang ZP, Zhang YL. How to assess the severity of atrophic gastritis. *World J Gastroenterol* 2011; 17(13): 1690-1693 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i13/1690.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i13.1690

INTRODUCTION

Atrophic gastritis (AG) is a histopathological entity that is characterized by chronic inflammation of the gastric mucosa with loss of gastric glandular cells and replacement by intestinal-type epithelium, pyloric-type glands, and fibrous tissue. Atrophy of the gastric mucosa is the endpoint of chronic processes, such as chronic gastritis associated with *Helicobacter pylori* (*H. pylori*) infection, other unidentified environmental factors, and autoimmunity directed against gastric glandular cells[1]. It has been established that people with AG have a high risk for gastric cancer[2,3], and it has been reported that about 10% of the patients with moderate-severe AG will develop gastric malignancies during a mean follow-up of 7.8 years[4]. Thus, the assessment of the severity of AG may be an important challenge for the management of these patients because its features (i.e. extension of atrophy and intestinal metaplasia, and hypochlorhydria) may be considered as potential surrogate markers for the increased risk for gastric cancer. Here, we demonstrate some methods used to assess the severity of AG.

DEFINITION AND CLASSIFICATION OF AG

Gastric mucosal atrophy is defined as the loss of appropriate glands, which occurs when glands damaged by inflammation are replaced either by connective tissue (scarring) or by glandular structures inappropriate for location (metaplasia). Most often, as in the antral mucosa, the metaplastic transformation assumes the phenotype of the glands lined by intestinal-type epithelium (IM), but in the oxyntic mucosa, it may also take the form of mucin-secreting antral glands (pseudopyloric metaplasia)[5]. Traditionally, AG can be divided into gastric body atrophy

and sinuses ventriculi atrophy: the former is mostly associated with autoimmune diseases, and the latter is often associated with *H. pylori* infection[6,7]. However, in general practice, the diagnosis of atrophy and IM is troublesome due to an unsatisfactory interobserver agreement among pathologists, therefore in 2000, an international group of pathologists from Atrophy Club reviewed once again the spectrum of gastric atrophy and IM, and proposed a simplified definition of atrophy, which includes a metaplastic and a non-metaplastic category, thus making metaplasia an absolute concept to demonstrate the severity of the disease[5].

CONVENTIONAL ENDOSCOPY AND AG

In 2003, the Chinese Society of Digestive Endoscopy established endoscopic criteria for chronic gastritis in Dalian meeting. The scar lesions were characterized by the following attributes: mucosal atrophy, granular mucosa, flattened folds, gray intestinal-type epithelium and blood vessel permeability. AG was classified into three patterns of ridges: (1) fine granular mucosa, permeability of some blood vessels and a single nodule of gray intestinal-type epithelium; (2) medium granular mucosa, permeability of blood vessels, multiple nodules of gray intestinal-type epithelium; and (3) coarse granular mucosa, blood vessels can be seen up to the surface, diffuse nodules of gray intestinal-type epithelium[8].

MAGNIFYING ENDOSCOPY AND AG

Magnifying endoscopy has been developed to visualize the microstructure of gastrointestinal surface mucosa and mucosal vascularity, which provides a magnified image of up to 200 times[9]. The pit patterns observed on the mucosal surface are considered to reflect the arrangement and structure of surface epithelia, morphology, number, distribution and function of glands, mucosal edema and inflammation, and vascular morphology, arrangement, number and distribution. The basic units of the microstructures on the surface of gastric mucosa are countless gastric pits that form gastric areas separated by minor gastric grooves (also called interval grooves). As the openings of glands, gastric pits are the first to undergo structural change due to gastric mucosal lesions. Yagi *et al*[10] thought that the presentation of gastric mucosal atrophy was that gastric pit became white, expanded in size, and was surrounded by areas of erythema. In the study of Sakaki *et al*, magnifying endoscopy patterns of gastric erosion pits were classified into six types: A (round spot pits), B (short rod pits), C (sparsely and thickly linear), D (patchy), E (villous) and F (unclear or disappearance of pits or abnormal hyperplasia blood capillary)[11]. Yuan *et al*[12] used magnifying endoscopy in combination with methylene blue staining to examinate the microstructures of gastric mucosa in 180 patients with gastric erosion. Their results showed that types A and B were found in normal gastric mucosa, while types C-F were found in gastric mucosa with active inflammation, atrophic inflammation, intestinal metaplasia and dysplasia of varying degrees. Type E mucosa (81.8%) suggested intestinal metaplasia, type F indicated existence of dysplasia (86.3%), and type F with abnormal hyperplasia blood capillary suggested dysplasia (89.9%).

MAGNIFYING NARROW-BAND IMAGING AND AG

Narrow-band imaging (NBI) is an endoscopic imaging technique for the enhanced visualization of mucosal microscopic structure and capillaries of the superficial mucosal layer. Images are obtained using narrower bands of red, blue and green filters, which are different from conventional red-green-blue filters[13]. Combining the NBI system and magnifying endoscopy allows for simple and clear visualization of microscopic structures of the superficial mucosa and its capillary patterns[14]. In the study of Tahara *et al*[15], gastric mucosal patterns seen with magnifying NBI in uninvolved gastric corpus were divided into the following categories: normal small, round pits with regular subepithelial capillary networks; type 1, slightly enlarged, round pits with unclear or irregular subepithelial capillary networks; type 2, obviously enlarged, oval or prolonged pits with increased density of irregular vessels; and type 3, well-demarcated oval or tubulovillous pits with clearly visible coiled or wavy vessels. They found that the mucosal patterns were associated with the degree of endoscopic gastric atrophy. As mucosal patterns advanced from normal to types 1, 2 and 3, the degree of endoscopic gastric mucosal atrophy increased simultaneously. The sensitivity and specificity for types 1, 2 and 3 for detection of *H. pylori* infection and type 3 for detection of intestinal metaplasia were 95.2%, 82.2%, 73.3%, and 95.6%, respectively. Uedo *et al*[16] found in their study that the appearance of a light blue crest on the epithelial surface was correlated with histological evidence of intestinal metaplasia with a sensitivity of 89% (95% CI: 83-96), specificity of 93% (95% CI: 88-97), positive predictive value of 91% (95% CI: 85-96), negative predictive value of 92% (95% CI: 87-97), and accuracy of 91% (95% CI: 88-95).

AUTO-FLUORESCENCE IMAGING VIDEOENDOSCOPY AND AG

Auto-fluorescence imaging (AFI) produces real-time pseudocolor images based on natural tissue auto-fluorescence emitted by light excitation from endogenous fluorophores such as collagen, nicotinamide, adenine dinucleotide, flavin and porphyrins. AFI enables the detection of mucosal features not visible with conventional endoscopy, therefore, it might improve the identification and characterization of the premalignant status in gastric mucosa[17,18].

The fluorescence is almost purple, weaker in the normal gastric gland mucosa than that in the pyloric gland mucosa.

When gastric mucosa is atrophic, the color is green, which is the same as that in the pyloric gland mucosa. Gastric biopsy is taken separately from purple and green region for pathological studies, and the green region is significantly increased in AG and intestinal metaplasia[19]. The extent of chronic atrophic fundal gastritis (CAFG) was considered to be the green areas in the gastric body and was classified into six categories by Inoue *et al*[20]: AF-C- Ⅰ, the entire gastric body appears purple to dark green; AF-C Ⅱ, a color border on the lesser curvature was observed at a lower part of the gastric body; AF-C-Ⅲ, a color border on the lesser curvature at an upper part of the gastric body; AF-O- Ⅰ, a color border between the lesser curvature and the anterior wall; AF-O-Ⅱ, a color border between the anterior wall and the greater curvature; and AF-O-Ⅲ, a color border on the greater curvature proximal to the lower gastric body. They found that the diagnostic accuracy of green areas in the gastric body of the patients in the activity, inflammation, atrophy and intestinal metaplasia was 64%, 93%, 88% and 81%, respectively. However, the diagnostic accuracy of AFI was not compared with that of white-light images in relation to the histology. Therefore, whether the accuracy of AFI is superior to that of white-light images is not known.

SERUM BIOMARKERS AND AG

Pepsinogen I and II

Pepsinogens (PGs) are aspartic proteinases that are mainly secreted by gastric cells. They can be immunologically classified into two major types: pepsinogen I (PG Ⅰ) and pepsinogen Ⅱ (PG Ⅱ). PGI is secreted only from the gastric fundic mucosa, whereas PG Ⅱ is secreted from the cardiac, fundic and antral mucosa of the stomach, and also from the duodenal mucosa[21]. Patients with gastric fundic atrophy have a lower mean serum PG Ⅰ concentration than those without atrophy. Both mucosal types secrete PG Ⅱ, however, serum PG Ⅱ levels remain stable or are increased during progression from a normal stomach to one with severe atrophy[22]. The net effects of severe atrophy on serum PG concentrations are lower PGI and a stable or increased PG Ⅱ, and this leads to a lower PG Ⅰ / Ⅱ ratio[22]. Ren *et al*[23] have confirmed a strong association between gastric fundic atrophy and PGs, as estimated by a low serum PGI and PG Ⅰ / Ⅱ ratio in a prospective study. They have found that compared to the subjects with a PG Ⅰ / Ⅱ ratio of > 4, those with a ratio ≤ 4 had hazard ratios (HRs) of 2.72 (95% CI: 1.77-4.20) and 2.12 (95% CI: 1.42-3.16) for non-cardiac and cardiac gastric adenocarcinoma, respectively. Storskrubb *et al*[24] found that the phenotype of gastritis is characterized by normal levels of serum PGs (PG Ⅰ ≥ 25 ng/mL and PG Ⅰ /PG Ⅱ ratio ≥ 3 indicate that the corpus mucosa is normal). For the diagnosis of atrophic corpus gastritis, three different criteria have been used as follows[25-27]: Mild: PG Ⅰ ≤ 70 ng/mL and PG Ⅰ / Ⅱ ratio ≤ 3.0; Moderate: PG Ⅰ ≤ 50 ng/mL and PG Ⅰ / Ⅱ ≤ 3.0; Strict: PG Ⅰ ≤ 30 ng/mL and PG Ⅰ / Ⅱ ≤ 2.0. Both cut-offs for PG Ⅰ and PG Ⅰ / Ⅱ should be fulfilled at the same time for each criterion.

Gastrin-17

Gastrin-17 (G-17) is secreted exclusively by the G-cells of the gastric antrum. The levels of G-17 are depressed in cases of atrophy in this area[28]. Leja *et al*[29] found that G-17 < 5 pmol/L is related to atrophy in the antral region (P = 0.007) with a 36.8% sensitivity and a 86.5% specificity. They indicated that G-17 used for the detection of atrophy in the antral part of the stomach requires further evaluations due to its low sensitivity.

H. pylori testing

H. pylori is now recognized as a major cause of gastric cancer and is classified as a group I carcinogen by the WHO[30,31]. *H. pylori* infection causes persistent chronic gastritis, which in susceptible individuals can progress to atrophy, intestinal metaplasia and dysplasia, and finally, intestinal-type gastric cancer[31,32]. Nearly all infected individuals (> 90%) exhibit *H. pylori*-specific IgG antibodies. Most (70%) of these individuals also exhibit IgA antibodies and H. Pylori proteins, including cytotoxin-associated gene A (CagA) protein and vacuolating cytotoxin A (VacA) protein. These proteins are used for *H. pylori* testing. A combined use of the serological biomarkers (PGI, PGII, G-17 and *H. pylori* antibodies) shows a high accuracy as a noninvasive method to diagnose gastric atrophy, which is common in the general population[23,24,33].

CONCLUSION

In the cases of AG, its severity is mainly related to the lifetime risk to develop gastric cancer, especially in terms of the degree and extension of mucosal damage. The application of conventional endoscopy, modern endoscopic technology and noninvasive methods is useful for the identification of those patients with atrophic gastritis at higher risk for gastric malignancies. Using these technologies to assess the severity of atrophic gastritis, interfering with the disease progress, and reversing gastric mucosal atrophy are the important issues for clinicians.

REFERENCES

1 **Yoshimura T**, Shimoyama T, Tanaka M, Sasaki Y, Fukuda S, Munakata A. Gastric mucosal inflammation and epithelial cell turnover are associated with gastric cancer in patients with Helicobacter pylori infection. *J Clin Pathol* 2000; **53**: 532-536

2 **Kurosawa M**, Kikuchi S, Inaba Y, Ishibashi T, Kobayashi F. Helicobacter pylori infection among Japanese children. *J Gastroenterol Hepatol* 2000; **15**: 1382-1385

3 **Kitahara F**, Shimazaki R, Sato T, Kojima Y, Morozumi A, Fujino MA. Severe atrophic gastritis with Helicobacter pylori infection and gastric cancer. *Gastric Cancer* 1998; **1**: 118-124

4 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789

5 **Rugge M**, Correa P, Dixon MF, Fiocca R, Hattori T, Lechago J, Leandro G, Price AB, Sipponen P, Solcia E, Watanabe H, Genta RM. Gastric mucosal atrophy: interobserver consistency using new criteria for classification and grading. *Aliment Pharmacol Ther* 2002; **16**: 1249-1259

6 **Checchi S**, Montanaro A, Pasqui L, Ciuoli C, Cevenini G, Sestini F, Fioravanti C, Pacini F. Serum ghrelin as a marker

of atrophic body gastritis in patients with parietal cell antibodies. *J Clin Endocrinol Metab* 2007; **92**: 4346-4351
7 **Veijola LI**, Oksanen AM, Sipponen PI, Rautelin HI. Association of autoimmune type atrophic corpus gastritis with Helicobacter pylori infection. *World J Gastroenterol* 2010; **16**: 83-88
8 Chinese Medical Association of Digestive Endoscopy. Endoscopic classification and trial standards on treatment of chronic gastritis. *Zhonghua Xiaohua Neijing Zazhi* 2004; **21**: 77-78
9 **Lee SH**, Ryu CB, Jang JY, Cho JY. [Magnifying endoscopy in upper gastrointestinal tract]. *Korean J Gastroenterol* 2006; **48**: 145-155
10 **Yagi K**, Nakamura A, Sekine A. Comparison between magnifying endoscopy and histological, culture and urease test findings from the gastric mucosa of the corpus. *Endoscopy* 2002; **34**: 376-381
11 **Yang JM**, Chen L, Fan YL, Li XH, Yu X, Fang DC. Endoscopic patterns of gastric mucosa and its clinicopathological significance. *World J Gastroenterol* 2003; **9**: 2552-2556
12 **Yuan HF**, Tang SB, Huang S, Xi JY. Diagnostic value of magnifying chromoendoscopy in gastric premalignant lesions. *Shijie Huaren Xiaohua Zazhi* 2008; **16**: 2052-2055
13 **Gono K**, Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, Yoshida S, Hamamoto Y, Endo T. Appearance of enhanced tissue features in narrow-band endoscopic imaging. *J Biomed Opt* 2004; **9**: 568-577
14 **Emura F**, Saito Y, Ikematsu H. Narrow-band imaging optical chromocolonoscopy: advantages and limitations. *World J Gastroenterol* 2008; **14**: 4867-4872
15 **Tahara T**, Shibata T, Nakamura M, Yoshioka D, Okubo M, Arisawa T, Hirata I. Gastric mucosal pattern by using magnifying narrow-band imaging endoscopy clearly distinguishes histological and serological severity of chronic gastritis. *Gastrointest Endosc* 2009; **70**: 246-253
16 **Uedo N**, Ishihara R, Iishi H, Yamamoto S, Yamamoto S, Yamada T, Imanaka K, Takeuchi Y, Higashino K, Ishiguro S, Tatsuta M. A new method of diagnosing gastric intestinal metaplasia: narrow-band imaging with magnifying endoscopy. *Endoscopy* 2006; **38**: 819-824
17 **Haringsma J**, Tytgat GN, Yano H, Iishi H, Tatsuta M, Ogihara T, Watanabe H, Sato N, Marcon N, Wilson BC, Cline RW. Autofluorescence endoscopy: feasibility of detection of GI neoplasms unapparent to white light endoscopy with an evolving technology. *Gastrointest Endosc* 2001; **53**: 642-650
18 **Kara MA**, Bergman JJ. Autofluorescence imaging and narrow-band imaging for the detection of early neoplasia in patients with Barrett's esophagus. *Endoscopy* 2006; **38**: 627-631
19 **Kato M**, Uedo N, Ishihara R, Kizu T, Chatani R, Inoue T, Masuda E, Tatsumi K, Takeuchi Y, Higashino K, Iishi H, Tomita Y, Tatsuta M. Analysis of the color patterns of early gastric cancer using an autofluorescence imaging video endoscopy system. *Gastric Cancer* 2009; **12**: 219-224
20 **Inoue T**, Uedo N, Ishihara R, Kawaguchi T, Kawada N, Chatani R, Kizu T, Tamai C, Takeuchi Y, Higashino K, Iishi H, Tatsuta M, Tomita Y, Tóth E. Autofluorescence imaging videoendoscopy in the diagnosis of chronic atrophic fundal gastritis. *J Gastroenterol* 2010; **45**: 45-51
21 **Samloff IM**, Taggart RT. Pepsinogens, pepsins, and peptic ulcer. *Clin Invest Med* 1987; **10**: 215-221
22 **Samloff IM**, Varis K, Ihamaki T, Siurala M, Rotter JI. Relationships among serum pepsinogen I, serum pepsinogen II, and gastric mucosal histology. A study in relatives of patients with pernicious anemia. *Gastroenterology* 1982; **83**: 204-209
23 **Ren JS**, Kamangar F, Qiao YL, Taylor PR, Liang H, Dawsey SM, Liu B, Fan JH, Abnet CC. Serum pepsinogens and risk of gastric and oesophageal cancers in the General Population Nutrition Intervention Trial cohort. *Gut* 2009; **58**: 636-642
24 **Storskrubb T**, Aro P, Ronkainen J, Sipponen P, Nyhlin H, Talley NJ, Engstrand L, Stolte M, Vieth M, Walker M, Agréus L. Serum biomarkers provide an accurate method for diagnosis of atrophic gastritis in a general population: The Kalixanda study. *Scand J Gastroenterol* 2008; **43**: 1448-1455
25 **Miki K**, Morita M, Sasajima M, Hoshina R, Kanda E, Urita Y. Usefulness of gastric cancer screening using the serum pepsinogen test method. *Am J Gastroenterol* 2003; **98**: 735-739
26 **Hattori Y**, Tashiro H, Kawamoto T, Kodama Y. Sensitivity and specificity of mass screening for gastric cancer using the measurment of serum pepsinogens. *Jpn J Cancer Res* 1995; **86**: 1210-1215
27 **Oishi Y**, Kiyohara Y, Kubo M, Tanaka K, Tanizaki Y, Ninomiya T, Doi Y, Shikata K, Yonemoto K, Shirota T, Matsumoto T, Iida M. The serum pepsinogen test as a predictor of gastric cancer: the Hisayama study. *Am J Epidemiol* 2006; **163**: 629-637
28 **Sipponen P**, Mäki T, Ranta P, Linnala A, Kääriäinen I, Helske T, Suovaniemi O, Härkönen M. Application of blood levels of gastrin-17, pepsinogen I and *H.pylori* antibody for nonendoscopic diagnosis of atrophic gastritis. Available from: URL: http://www.biohit.com/pdf/ddwsip.pdf
29 **Leja M**, Kupcinskas L, Funka K, Sudraba A, Jonaitis L, Ivanauskas A, Janciauskas D, Kiudelis G, Chiu HM, Lin JT. The validity of a biomarker method for indirect detection of gastric mucosal atrophy versus standard histopathology. *Dig Dis Sci* 2009; **54**: 2377-2384
30 **Schistosomes**, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994. *IARC Monogr Eval Carcinog Risks Hum* 1994; **61**: 1-241
31 **Fox JG**, Wang TC. Helicobacter pylori-not a good bug after all! *N Engl J Med* 2001; **345**: 829-832
32 **Correa P**. A human model of gastric carcinogenesis. *Cancer Res* 1988; **48**: 3554-3560
33 **Weck MN**, Stegmaier C, Rothenbacher D, Brenner H. Epidemiology of chronic atrophic gastritis: population-based study among 9444 older adults from Germany. *Aliment Pharmacol Ther* 2007; **26**: 879-887

S- Editor Sun H **L- Editor** Ma JY **E- Editor** Ma WH