How to assess the severity of atrophic gastritis

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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[8].

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[9].

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[9] 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)[10]. Yuan et al[8] used magnifying endoscopy in combination with methylene blue staining to examine 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 autofluorescence 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 (CAF G) 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). PG I 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[20]. 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[20]. The net effects of severe atrophy on serum PG concentrations are lower PG I and a stable or increased PG II, and this leads to a lower PG I/II ratio[20]. Ren et al[21] 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[21] 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) that indicate the corpus mucosa is normal). For the diagnosis of atrophic corpus gastritis, three different criteria have been used as follows[22-23]: 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[20]. Leja et al[22] 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[20,21]. 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[22,23]. 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[24-31].

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.

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