Gut Microbiota for Integrative Wellness

REVIEW

# Practice and thinking on the traditional Chinese medicine treatment of chronic atrophic gastritis based on pathological evaluation

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**ABSTRACT**

Chronic atrophic gastritis is a precancerous gastric disease with intestinal epithelial hyperplasia and heterogeneous proliferation based on mucosal atrophy. In recent years, the international guidelines and consensus on the treatment of precancerous gastric disease have been gradually updated, emphasizing the treatment of precancerous gastric disease and lesions based on the pathological changes as the outcome. Chinese medicine is widely used in the clinical treatment of chronic atrophic gastritis, but there are fewer research ideas of Chinese medicine based on the pathological evaluation of the results. In this article, the pathological concepts related to chronic atrophic gastritis and the clinical research ideas and practice strategies of traditional Chinese medicine based on the evaluation of pathological outcomes are compiled.

**Key words:** chronic atrophic gastritis, precancerous lesions of the stomach, pathological histology, Chinese medicine intervention

## INTRODUCTION

Chronic atrophic gastritis (CAG) is a type of chronic gastritis that refers to chronic gastric disease with or without fibrous replacement, intestinal glandular hyperplasia, and/or pseudopyloric glandular hyperplasia due to repeated damage to the epithelium of the gastric mucosa, resulting in a reduction of glands in the lamina propria.[1] CAG, intestinal metaplasia (IM) and concomitant dysplasia (Dys) are closely related to the development of gastric cancer, and the pattern "normal gastric mucosa-chronic superficial gastritis-gastritic atrophy-IM-Dys-infiltrating gastric carcinoma" is considered the classic pattern of transformation of normal gastric mucosa into gastric cancer of intestinal type.[2] The pathological state of gastric mucosa in patients is closely related to the risk of carcinogenesis. One study showed that the annual crude incidence of gastric cancer was 20/100,000 in the population with normal gastric mucosa, 59/100,000 in the group with non-atrophic gastritis, 100/100,000 in the group gastritic atrophy, 129/100,000 in the group IM, and 263/100,000 in the group Dys.[3] Clinical evidence also shows the possibility of slow regression of the cascade lesions of gastric cancer.[4] This provides an exceptional opportunity for traditional Chinese medicine (TCM) intervention in atrophic gastritis.

## IMPORTANT PATHOLOGICAL CONDITIONS OF CHRONIC ATROPHIC GASTRITIS

### *Glandular atrophy and intestinal epithelial metaplasia*

Atrophic gastritis, can be divided into two categories: (1)

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Glandular atrophy: the number of glands is reduced and replaced by fibrous tissue without significant change in the original epithelial phenotype. (2) Metaplasia: the number of glands is not necessarily reduced, but the glands in a given area are replaced by IM and pseudopyloric pseudocortex metaplasia. The delineation of the presence and severity of CAG should be based on the loss of glands, *i.e.*, chemosis is included in this diagnostic system, and the number of glands is not necessarily reduced after metaplasia, but there is a phenotypic change of glands in the region, which also falls under the category of atrophy. The diagnosis of atrophy includes endoscopic diagnosis and pathological-histological diagnosis and relies more on pathological-histological diagnosis.[5] Conventional wisdom states that the accuracy of endoscopic diagnosis of atrophy is limited by the experience of the endoscopist. There are also some findings suggesting that the endoscopic diagnosis of atrophy is more consistent with the pathologic diagnosis.[6,7]

IM is the most reliable marker of gastric mucosal atrophy.[8] IM is classified into 3 subtypes based on morphology and mucin staining. Type I is complete and morphologically resembles small intestinal epithelium. It is characterized by non-secretory absorptive cells and sialomucin secreting goblet cells. Type II is characterized by few absorptive cells, columnar cells secreting neutral and acid sialomucin, and goblet cells secreting mainly sialomucin but occasionally sulphomucin. Type III is characterized columnar cells secreting predominantly sulphomucin and goblet cells secreting sialomucin or sulphomucin. Type II and Type III are regarded as Incomplete IM. [9] Cohort studies have shown that the type III IM has a higher risk of carcinoma.[10,11] It has also been pointed out that subtype diagnosis of IM requires the use of immunohistochemical techniques, which are not commonly used in routine diagnosis and are highly subjective in diagnosis, and their value for clinical application is controversial.[12]

### *Dysplasia*

Dys is defined as an epithelium with significant cellular and/or structural abnormalities in the manner of tumor growth without infiltration of the lamina propria. In the latest World Health Organization (WHO) guidelines, gastric intraepithelial neoplasia (GIN) is still referred to with a similar meaning to heterogeneous hyperplasia.[13] The Chinese consensus on the diagnostic pathology of gastric mucosal biopsy for chronic gastritis and epithelial tumors recommended the use of the diagnostic term "intraepithelial tumor" and clarified that "atypia" and "reactive atypia" are reactive epithelial hyperplasia caused by inflammation without tumor.[14] This standardized the use of diagnostic terms for clinical gastric mucosa and clarified that GIN/Dys is a precancerous lesion of the stomach.

## PATHOLOGICAL-HISTOLOGICAL EVALUATION METHOD OF CHRONIC ATROPHIC GASTRITIS CONDITION

### *Evaluation of mucosal atrophy and intestinal metaplasia*

Atrophy and IM can be classified as mild, moderate or severe according to the visual analog scale proposed by the Sydney system.[1] In addition to the degree of lesion, the extent of atrophy and IM also correlates with the risk of cancer development. Previous studies have shown that the degree and extent of gastric mucosal atrophy and IM are closely related to disease development, and the more extensive the lesion, the higher the risk of gastric cancer. In a Japanese retrospective cohort study, after a mean follow-up of 6.2 years, the 5-year cumulative incidence of gastric adenocarcinoma was found to be 1.5% in the group without mucosal atrophy, 5.3% in the group with limited IM of the gastric sinus, and 9.8% in the group with diffuse IM of the gastric body.[15] Therefore, diagnosis of the grade of the focal lesion alone cannot accurately assess the patient's prognosis. In 2005, international gastroenterologists and pathologists jointly proposed a staging system for gastritis: the Operative Link for Gastritis Assessment (OLGA).[16] This score evaluates the risk of carcinoma in gastritis based on the extent and degree of atrophic lesions. Interobserver agreement was low for histopathologic diagnosis of atrophy and high for histopathologic diagnosis of IM. Therefore, the International Working Group on Atrophy proposed the "Operative link for gastric intestinal metaplasia evaluation (OLGIM)" staging and grading system at its meeting in 2010. The risk of gastritis carcinoma was evaluated by combining the extent and grade of IM.[17] Follow-up studies have confirmed that the OLGA/OLGIM system can distinguish people at high risk for gastric cancer and that patients may benefit from surveillance.[18,19]

### *Evaluation of Dysplasia*

GIN/Dys is currently recommended as high or low grade. Epidemiological surveys have shown that the incidence of Dys in Europe and the United States ranges from 0.5% to 3.75%, while in regions with a high prevalence of gastric cancer, such as Colombia and China, the incidence reaches 9% to 20%.[20] Both low-grade and high-grade Dys can develop into gastric cancer. The probability of malignancy in high-grade Dys between 4 and 48 months has been shown to be 60% to 85%.[21] In contrast to high-grade Dys, patients with low-grade Dys are less likely to develop gastric cancer. About 6.6% to 8.8% of low-grade Dys lesions progress to high-grade Dys and invasive carcinoma, 38% to 75% regress, and 19% to 50% remain unchanged.[4,22]

## OBJECTIVE EVALUATION AND PRACTICE OF CHINESE MEDICINE IN THE TREATMENT OF CHRONIC ATROPHIC GASTRITIS

### *Current status of clinical treatment of chronic atrophic gastritis*

The currently recognized important etiology of CAG is helicobacter pylori (HP) infection, which causes tissue inflammation, cellular autophagy, oxidative stress, and other reactions important for the progression of this cascade pattern.[23,24] Currently, the most important intervention against the gastric cancer cascade is HP eradication therapy. Currently, there is ample evidence that eradication of HP can delay or prevent the onset and progression of gastric mucosal atrophy and/or IM,[25–28] and prevent the development of heterochronic gastric cancer,[29] but the specific population that benefits from eradication therapy remains controversial. A meta-study has shown that HP testing with an eradication strategy reduces the incidence of gastric cancer in Asians with asymptomatic infection, but these data cannot necessarily be extrapolated to other populations.[30] A recent prospective, double-blind, placebo-controlled, randomized trial of 470 patients with early gastric cancer or high-grade adenoma treated with endoscopic resection followed by HP eradication or placebo demonstrated that HP eradication after endoscopic submucosal dissection (ESD) prevented the development of heterochronous gastric cancer and that HP eradication therapy still benefited patients after early gastric cancer resection.[31] However, there are studies with conflicting results, and another study on long-term follow-up after endoscopic treatment of patients with early gastric cancer showed that HP eradication did not reduce the incidence of heterochronous gastric cancer and that severe mucosal atrophy at baseline and follow-up of more than 5 years were independent risk factors for the development of heterochronous gastric cancer.[32] It is obvious that the progression of CAG is related to multiple factors and a single treatment may have difficulty in improving the prognosis of patients.

### *Utilization of the advantages of the treatment with Chinese medicine*

The advantage of TCM treatment of CAG lies in the concept of the patient as the main actor of the treatment. The chronic course of the disease, the patient's symptoms are complex, and the recurrence of long-term symptoms means that some patients are often associated with emotional and sleep problems. A cross-sectional survey in Japan showed that young women (< 50 years old) with CAG had an increased risk of psychological distress and depressive mood, and those with HP-positive seropositivity had the highest risk of psychological distress and depression.[33] Patients in the early stages of precancerous gastric disease may experience anxiety due to doubts about the fate of the disease, and that at this time it is difficult to meet the clinical needs of patients with symptomatic treatment by Western medicine alone. The advantage of TCM treatment is that it puts the patient at the center of treatment, treats the complex symptoms of body and mind, pays attention to the basic disease mechanism of "stasis" and "deficiency" throughout the process, and strengthens the psychological care of patients with precancerous gastric disease, which can help improve the quality of life and prevent the recurrence of symptoms. Recurrence of symptoms. The more complex the mechanism of chronic disease is, the more we can start from the main disease mechanism to reflect the advantages of TCM in simplifying treatment and coping with complexity with simplicity.

### *Significance and problems of pathological evaluation of traditional Chinese medicine treatment*

Several studies[34,35] have shown that TCM is a viable intervention for the treatment of CAG, but all of them lacked a rigorous pathological-histological evaluation. Some systematic evaluations of TCM treatments, such as the Xinkaikujiang method, the method for promoting qi and invigorating blood, and the method for dissolving blood stasis and detoxifying toxins, have confirmed the efficacy of TCM in treating CAG, but the quality of the evidence is low.[36–38] Outcome assessment of clinical trials includes biological assessment, health economic assessment, and quality of life assessment. Biological assessment refers to clinical outcomes or outcome proxies that reflect the progression of the patient's pathology and respond directly to disease regression. Biological assessment of CAG often revolves around outcome indicators such as the number of glandular atrophy, heterogeneous hyperplasia, and incidence of gastric cancer, and the disease progresses slowly. Follow-up studies published internationally on CAG focus on long-term outcomes. This requires the design of long-term follow-up studies with internationally accepted pathological evaluation criteria to demonstrate the effect of TCM on disease regression. However, the advantage of TCM treatment is the flexibility of diagnosis and treatment according to the patient's symptoms, and it is inevitable that the treatment regimen will change during the long follow-up period, which will affect the evaluation of efficacy.

The ultimate goal of TCM treatment is to maintain the patient's physical condition and mental function in a satisfactory state and to live a high-quality life. In addition to the pathological changes of the mucous membranes, CAG patients also have "psychological" and "social" problems. Some survival quality scales including multiple assessments from physiological domain, psychological domain and social environment

domain have been widely used to clinically evaluate the effectiveness of CAG before and after treatment, which can better reflect the benefits of TCM treatment in a multidimensional way. The chronic gastritis module of the Spleen and Gastric System Disease Scale developed by Liu Fengbin *et al.* evaluates the efficacy of TCM treatment of chronic gastritis in four domains (the physiological domain, the independence domain, the psychological domain, and the social environment domain) and in seven aspects (including energy and form, pain and discomfort, digestive function, and psychological aspects).[39] Liu *et al.*[40] developed an outcome scale for patients with precancerous lesions in CAG that incorporates "form and mind-related" (physiological domain), "seven emotions-related" (psychological domain), "heavenly and human-related" (social-environmental domain), and other TCM theories. However, the clinical applicability of the above scales needs further validation, and there is still a lack of recognized and widely used CAG outcome scales.

In conclusion, pathological histology is the golden indicator for the diagnosis of CAG and is closely related to the prognosis of CAG patients. In order to prove the clinical efficacy of TCM in the treatment of this disease, it is necessary to grasp the essence of the pathological changes of the disease and position TCM interventions. Studies to improve patient prognosis, with the main outcome indicators using internationally recognized pathological assessment methods. Of course, it is biased to evaluate the pathophysiologic condition of patients based only on pathologic tissue changes. The evaluation of the disease-related outcome scale may serve to improve the survival treatment of patients, but it is still recommended to include the evaluation of mucosa and pathology. There are differences in the treatment systems of TCM and Western medicine, and the existing efficacy evaluation system limits the therapeutic advantages of TCM, but exploring the nature of disease is the common pursuit of "truth" in medicine. Evaluation based on the pathophysiology of the disease is the basic requirement for the evaluation of efficacy. Evaluation of CAG treatment with TCM needs further development based on improved pathological histology and appropriate outcome assessment tools that can reflect the benefits of TCM treatment.

## DECLARATIONS

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