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Research Progress of Traditional Chinese and Western Medicine on Precancerous Lesions of Gastric Cancer

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Abstract: ***Precancerous lesions of gastric cancer (PLGC) are pathological changes arising from multiple pathogenic factors, characterized by intestinal metaplasia, dysplasia, or intraepithelial neoplasia superimposed on chronic atrophic gastritis (CAG). They represent a critical transitional stage from normal gastric mucosa to gastric cancer. Currently, modern medicine has made certain progress in elucidating the pathogenic factors and pathogenesis of PLGC. Treatment primarily involves eradication of Helicobacter pylori (Hp), acid suppression and gastric mucosal protection, supplementation with vitamins and folic acid, and endoscopic surgical procedures; however, it remains difficult to reverse the pathological alterations. In recent years, traditional Chinese medicine (TCM), through syndrome differentiation and treatment as well as comprehensive intervention, has achieved relatively satisfactory therapeutic efficacy in managing PLGC, demonstrating its potential advantages. This article reviews and summarizes the research on the diagnosis and treatment of PLGC with traditional Chinese and Western medicine in recent years, aiming to provide a reference for further promoting the clinical application and research of TCM in this field.***

Keywords: Precancerous lesions of gastric cancer, Traditional Chinese and Western medicine, Review.

1. Introduction

Gastric cancer (GC) is one of the most common malignant tumors worldwide, with both its incidence and mortality ranking fifth globally; it is the fifth most common cancer and the fourth leading cause of cancer death [1]. Recent studies show that the numbers of new cases and deaths of gastric cancer in China account for 37.02% and 39.44% of the global totals, respectively, ranking fifth in incidence and third in mortality among all cancers in China, which seriously endangers national health and poses a tremendous challenge to public health [2] According to the Correa cascade, normal gastric mucosa progresses from chronic gastritis to chronic atrophic gastritis, then to intestinal metaplasia or intraepithelial neoplasia, and ultimately to GC, undergoing a complex series of transformations [3]. Among these, intestinal metaplasia, dysplasia, or intraepithelial neoplasia occurring on the basis of chronic atrophic gastritis (CAG) is regarded as precancerous lesions of gastric cancer (PLGC) [4], a critical transitional stage from normal gastric mucosa to gastric cancer. Therefore, how to effectively treat PLGC and promptly block the gastritis-to-cancer transformation of the stomach is of paramount importance. Currently, modern medicine diagnoses this disease mainly based on endoscopic examination and histopathological examination of the gastric mucosa [5], and there is still a lack of ideal treatment. The measures adopted mostly include eradication of Helicobacter pylori infection, suppression of gastric acid secretion, appropriate supplementation with multivitamins and selenium-containing drugs, endoscopic treatment, or surgical resection [6]. In recent years, traditional Chinese medicine (TCM) has achieved relatively satisfactory efficacy in the treatment of PLGC, which can not only improve the clinical symptoms of patients but also exert a certain reversal effect on the pathological changes of PLGC [7]. Therefore, this article reviews the research progress of traditional Chinese and Western medicine in the treatment of PLGC in recent years, as detailed below.

2. Modern Medicine's Understanding of PLGC

PLGC is a critical pathological stage in the transformation from normal gastric mucosa to GC and represents a key focus in the secondary prevention of GC. Its clinical manifestations are non-specific; patients may present with symptoms such as gastric distension, stomach pain, and belching, or they may remain asymptomatic. Over the past few decades, the global incidence of PLGC has been gradually rising, with a trend toward onset at a younger age [8]. Although modern medicine has made some progress in understanding the pathogenic factors and pathogenesis of PLGC, a satisfactory treatment remains lacking.

2.1 Pathogenic Factors

PLGC is not the result of a single factor but a pathological change caused by the interplay of multiple factors, multiple targets, and multiple mechanisms.

2.1.1 Helicobacter pylori Infection

Helicobacter pylori (H. pylori) is the primary pathogenic factor for PLGC and has been classified as a Group I carcinogen by the World Health Organization [9]. H. pylori contributes to pathogenesis by directly damaging the gastric mucosa and inducing chronic inflammatory responses. The infection can release various pro-inflammatory cytokines, such as IL-8, IL-1, and TNF-α, leading to a persistent inflammatory state that aggravates gastric mucosal injury. Meanwhile, H. pylori infection disrupts the expression and function of mucins (e.g., MUC5A and MUC1), compromising the integrity of the gastric mucosal barrier and thereby facilitating further bacterial colonization [10]. Virulence factors produced by H. pylori, such as cytotoxin-associated

gene A (CagA) and vacuolating cytotoxin A (VacA), play a critical role in the pathogenic process. CagA activates oncogenic signaling pathways including MAPK and PI3K, causing cellular morphological changes and loss of cell polarity, thus initiating carcinogenesis. VacA, on the other hand, disrupts the gastric epithelial barrier function by forming membrane channels and exerts either pro-apoptotic or anti-apoptotic effects depending on the microenvironmental conditions. Furthermore, VacA can interfere with the function of immune cells such as T cells, helping H. pylori evade immune clearance [11]. These mechanisms collectively lead to sustained gastric mucosal damage, chronic inflammation, and an increased risk of gastric cancer.

2.1.2 Duodenogastric Reflux

Duodenogastric reflux is an important risk factor for PLGC and is associated with the reflux of duodenal contents (bile acids, pancreatic enzymes, etc.) into the stomach due to pyloric sphincter dysfunction. Multiple studies worldwide have confirmed that bile reflux significantly increases the risk of PLGC progression, regardless of the presence of H. pylori infection. Bile acids promote the development of PLGC by activating multiple signaling pathways (e.g., miR-92a-15p/FoxD1/NF-κB/FXR/SHP) [12], among which the FoxO4/CDX2 pathway directly drives the process of gastric mucosal intestinal metaplasia by upregulating the expression of the intestinal metaplasia marker CDX2. Collectively, these mechanisms establish duodenogastric reflux as a key pathological factor that promotes the occurrence and progression of PLGC and its eventual evolution into gastric cancer.

2.1.3 Unhealthy Dietary and Lifestyle Habits

High-salt diet, preserved foods, smoking, and alcohol consumption are important risk factors for PLGC. Studies have shown that the high incidence of gastric cancer in East Asia is closely associated with the intake of preserved foods, and heavy consumption of such foods can increase the risk of gastric cancer by 1.24-fold [13]. The high salt and nitrites contained in these foods can generate the potent carcinogen N-nitrosamines, damage the gastric mucosa, and promote Helicobacter pylori infection. Carcinogens in tobacco can directly damage the DNA of gastric epithelial cells. The alcohol metabolite acetaldehyde can interfere with DNA repair, and long-term alcohol consumption significantly increases the risk of both cardia and non-cardia gastric cancer. These unhealthy habits act synergistically through multiple mechanisms, jointly promoting the occurrence and development of PLGC and gastric cancer.

2.1.4 Other Factors

Immune dysfunction (such as autoimmune gastritis), long-term use of non-steroidal anti-inflammatory drugs (NSAIDs), and advanced age (>50 years) can all damage the gastric mucosa through various pathways [5]. In recent years, new progress has been made in research on the gastric microbiota. In addition to H. pylori, other Helicobacter species (such as Helicobacter suis and Helicobacter felis) have been found to co-infect approximately 12% of patients. However, it remains difficult to determine whether changes in the microbiota are a cause or a consequence of the disease, and the specific underlying mechanisms still require further investigation.

2.2 Diagnosis

The diagnosis and assessment of PLGC primarily involve two approaches. The first is invasive gastroscopy, which allows the collection of gastric mucosal specimens for pathological examination and is considered the “gold standard” for diagnosis, offering high accuracy and reliability. The second is a non-invasive method, namely the detection of serum pepsinogen I (PG I), pepsinogen II (PG II), the PG I/PG II ratio, and gastrin-17 (G-17). These serve as serological markers of gastric mucosal atrophy and can be used as a preliminary screening method for atrophic gastritis [14].

2.3 Treatment Methods

Currently, Western medical treatment for PLGC primarily includes eradication of H. pylori, suppression of gastric acid secretion, appropriate supplementation with multivitamins and folic acid, and endoscopic or surgical intervention. There is as yet no specific treatment that can reverse this disease.

2.3.1 Endoscopic Treatment

Endoscopic treatment mainly comprises endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). EMR is suitable for patients with small lesions and shallow invasion, and is performed by resecting the diseased mucosal tissue. ESD is applicable for patients with larger lesions and deeper invasion, allowing complete en bloc dissection of the diseased mucosa under endoscopy, thereby reducing the risk of recurrence [15]. Both techniques can radically remove early GC lesions and offer advantages such as minimal damage to gastric anatomy, rapid recovery, low cost, and fewer postoperative complications. In the treatment of PLGC, ESD can accomplish en bloc dissection of large lesions with a success rate of up to 96% (reported as “面积可达96%” in the original text, which likely refers to an en bloc resection rate rather than a literal area percentage), provide accurate pathological assessment, and reduce the recurrence rate. Its safety and feasibility have been well recognized [16].

2.3.2 Pharmacological Treatment

Currently, the clinical treatment of PLGC is primarily centered on the eradication of H. pylori, combined with acid suppression, gastric mucosal protection, and folic acid supplementation. For H. pylori-positive PLGC patients, triple therapy or quadruple therapy is commonly used in clinical practice. Triple therapy consists of a proton pump inhibitor (PPI) plus two antibiotics, while quadruple therapy consists of a PPI, a bismuth agent, and two antibiotics [17]. The development of PLGC is mainly attributed to gastric mucosal damage caused by multiple factors. Mucosal protective agents (such as teprenone and rebamipide) can promote mucosal repair and therefore have therapeutic significance for PLGC. Prokinetic agents (such as mosapride and domperidone) can enhance gastrointestinal motility, alleviate bile reflux, inhibit gastric acid secretion, and reduce the erosion of the gastric

mucosa by digestive fluids. Studies have shown that the combination of a prokinetic agent and a mucosal protective agent can achieve a synergistic effect of "1 + 1 > 2." For instance, the combined use of mosapride and rebamipide not only promotes gastrointestinal motility and reinforces gastric mucosal protective mechanisms, but also increases gastric mucosal blood flow and enhances the degree of mucosal repair [18]. For patients with excessive gastric acid secretion, PPIs and H2 receptor antagonists are applied to suppress acid secretion and reduce gastric mucosal injury. In addition, supplementation with folic acid and vitamin B12 can also serve as adjuvant therapy for PLGC [19].

2.3.3 Lifestyle Intervention

The occurrence and progression of PLGC are closely related to personal lifestyle habits such as high salt intake, long-term smoking, and alcohol consumption, as well as negative emotions including depression, anxiety, and irritability. Therefore, patients with PLGC should pay attention to lifestyle modifications, adopt a reasonable diet, actively engage in physical exercise, and maintain a cheerful mood, which may improve their early-stage symptoms.

3. Understanding of PLGC in Traditional Chinese Medicine

3.1 Etiology and Pathogenesis

There is no direct disease name for PLGC in traditional Chinese medicine (TCM). Based on its clinical manifestations such as gastric distension, belching, and poor appetite, it can be classified into the categories of "gastric stuffiness" (wei pi) and "gastric noisy" (cao za), among others. As stated in the Yellow Emperor's Inner Canon, "When healthy qi exists within, pathogenic factors cannot invade; where pathogenic factors gather, qi must be deficient." TCM holds that deficiency of healthy qi is the internal condition for disease onset. When healthy qi is deficient and pathogenic factors invade, the spleen and stomach are impaired, leading to dysfunction of the spleen and stomach in transportation. This further results in qi dynamic obstruction, water-dampness retention, internal production of phlegm-turbidity, and blood stasis obstructing the collaterals. The pathological products become intertwined and transform into toxic pathogens, with epigastric distension and fullness, belching, and poor appetite as the external manifestations. The spleen and stomach are "the source of qi and blood production" and "the foundation of postnatal health." When the spleen and stomach are weak and fail to transport and transform properly, the source of qi and blood production is insufficient, and the stomach collaterals lose nourishment, presenting as changes in the color, nature, and morphology of the mucosa and mucosal pool under gastroscopy [20].

Since modern times, many TCM practitioners have proposed more comprehensive insights into the etiology and pathogenesis of PLGC. National Master of TCM Li Diangui creatively advanced the "turbid toxin theory," suggesting that turbid toxin is a sticky, turbid, and filthy substance formed when dampness turbidity and food turbidity accumulate over time and transform into heat. It lingers in the body, damages the spleen and stomach, and runs through the entire process of the occurrence and progression of PLGC. Treatment should focus on resolving turbidity and detoxifying [21-22]. National Master of TCM Lu Zhizheng, based on years of clinical experience, condensed his academic thought into the "Eighteen-Character Formula," namely: "Uphold the center, mobilize the four sides, harmonize the emotions, regulate ascending and descending, attend to moistening and dryness, normalize intake and transformation." Professor Lu emphasizes that the treatment of PLGC should be grounded in the "center"—the spleen and stomach—and pay close attention to the relationships between the liver and stomach, liver and spleen, and spleen and stomach. It should regulate the ascending and descending of spleen-stomach qi movement, with concurrent regulation of qi and blood, interdependence of ascending and descending, balance of moistening and dryness, and mutual support of yin and yang, so as to achieve "normal intake and transformation" of the spleen and stomach and restore their receiving and transporting functions [23]. Professor Tang Xudong proposed the theory of "regulating the middle and restoring balance," emphasizing that the treatment of spleen-stomach diseases should focus on the core role of the spleen and stomach functions in the middle burner, while restoring the normal ascending and descending of qi dynamic in the middle burner and the coordination of the five zang organs [24-26].

In summary, PLGC is located in the stomach and is closely related to the liver and spleen. Its etiology and pathogenesis are complex, characterized by a syndrome of deficiency in origin and excess in superficiality with intermingled deficiency and excess. Spleen-stomach weakness constitutes the root (ben), while blood stasis, toxic turbidity, phlegm-dampness, and other pathogenic excesses constitute the branch (biao).

3.2 Syndrome Differentiation and Treatment

Syndrome differentiation and treatment is the primary principle of TCM in diagnosing and treating diseases. Currently, there is no unified TCM syndrome classification for PLGC. Since PLGC frequently accompanies CAG, its macroscopic syndrome differentiation is similar to that of CAG. Referring to the Expert Consensus on the Integrated Traditional Chinese and Western Medicine Diagnosis and Treatment of Chronic Atrophic Gastritis (2025) [27] and the retrospective cohort study of PLGC patients by Huang Yuping et al. [28], the widely recognized syndrome patterns are liver-stomach disharmony pattern, spleen-stomach dampness-heat pattern, stomach collateral stasis pattern, spleen-stomach weakness pattern (spleen-stomach yang deficiency pattern), and stomach yin deficiency pattern [14].

3.2.1 Spleen-Stomach Weakness Pattern (Spleen-Stomach Yang Deficiency Pattern)

Li Dongyuan recorded in the Treatise on the Spleen and Stomach: "When the spleen and stomach qi is uninjured, original qi is abundant and can be nourished. If the foundation of stomach qi is weak and one overeats, the spleen and stomach qi will be damaged, original qi will be insufficient, and all diseases will arise." This shows that the healthy functioning of the spleen and stomach is closely related to the vital activities of the body. The Spiritual Pivot (Lingshu)

states: “The initial production of accumulation arises from cold; reversal of qi then leads to the formation of accumulation.” As the saying goes, visceral cold gives rise to distension and fullness; when yang is deficient, cold arises from within. Accordingly, the main symptoms of this pattern include epigastric distension, fullness, and discomfort or accompanying dull pain that lasts for a relatively long time, aggravated by hunger or exposure to cold and relieved after eating, with a preference for warmth and pressure, regurgitation of clear fluid, fatigue, and lack of strength. The tongue coating is relatively white, and the pulse is weak. Under gastroscopy, the mucosa in this pattern becomes thinner, appears pale or grayish-white, and may show edema or a large amount of thin mucus; submucosal blood vessels are clearly visible, and gastric peristalsis is weakened [14]. Treatment should focus on fortifying the spleen and harmonizing the stomach, warming the middle, and dissipating cold, with Huangqi Jianzhong Decoction (Astragalus Center-Fortifying Decoction) as the formula of choice. In a clinical study, Hong Wuhan found that Huangqi Jianzhong Decoction significantly improved the clinical symptoms of PLGC, and the reversal rates of CAG and gastric intestinal metaplasia (GM) were significantly superior to those in the control group ($P<0.05$). After treatment, IL-6, IL-8, and IL-1 levels were all significantly decreased compared with those before treatment [29]. Chinese patent medicines such as Weifuchun, Yangwei Granules, and Wenweishu Capsules can help relieve discomfort.

3.2.2 Liver-Stomach Disharmony Pattern

As recorded in the Spiritual Pivot (Lingshu): “If there is internal injury due to anxiety and anger, qi will rise counterflow; when qi rises counterflow, the six transport points become obstructed... and then accumulations form.” Among PLGC patients, the liver-stomach disharmony pattern accounts for a relatively large proportion, often resulting from chronic illness with excessive thinking, internal injury by the seven emotions, anxiety, pensiveness, and anger. The main clinical symptoms of this pattern include epigastric distension, fullness, pain, and discomfort, which can radiate to the back and both hypochondriac regions in severe cases, accompanied by belching, chest tightness, and sighing. These symptoms are induced or aggravated by emotional factors. The tongue coating is thin and white, and the pulse is wiry. Under gastroscopy, the mucosa shows acute active inflammatory reaction with relatively rapid peristalsis, possibly accompanied by bile reflux. The treatment principle is to soothe the liver, regulate qi, and disperse stuffiness. Liang Jingqiu et al. treated PLGC patients with the liver-stomach disharmony pattern using modified Chaihu Shugan Powder and Huagan Decoction, and found that the patients’ gastrin-17 (G-17) levels decreased significantly, while the PGI/PGII ratio increased significantly, thus delaying the progression of PLGC with good safety [30]. Professor Qian Huinan is adept at using medicinals that enter the liver meridian, such as Bupleuri Radix (Chaihu), Citri Reticulatae Pericarpium Viride (Qingpi), Toosendan Fructus (Chuanlianzi), and Cyperi Rhizoma (Xiangfu), to move qi and resolve constraint, soothe the liver, and harmonize the stomach, combined with medicinals such as Aucklandiae Radix (Muxiang), Mume Flos (Bai Meihua), Citri Sarcodactylis Fructus (Foshou), and Hordei Fructus Germinatus (Sheng Maiya) to rectify spleen-stomach qi stagnation, thereby moving qi and dispersing stuffiness [31]. In addition, Qizhi Weitong Granules and Jiawei Zuojin Pills are also optional medicines for this pattern.

3.2.3 Spleen-Stomach Dampness-Heat Pattern

This pattern is caused by the dysfunction of the spleen and stomach in transportation and transformation, leading to water-dampness retention and accumulation, which transforms into heat over time. The main symptoms include epigastric and abdominal stuffiness, oppression, and burning pain, poor appetite, halitosis, red tongue with yellow greasy coating, and a slippery rapid pulse. Under gastroscopy, the mucosa appears congested and edematous with obvious erosion, and the mucus is turbid and viscous. The treatment principle is to clear heat, resolve dampness, loosen the middle, and awaken the spleen, with Huanglian Wendan Decoction (Coptis Gallbladder-Warming Decoction) as the main formula. The Chinese patent medicine Sanjiu Weitai Granules is also a recommended medication. Furthermore, Zhang Dan et al. used the Huatan Xiaoyu Formula (Phlegm-Transforming and Stasis-Dispersing Formula) to treat PLGC patients and found that this formula not only alleviated symptoms such as epigastric distension, pain, and thirst, but also reduced the patients’ tumor marker levels and increased the reversal rate of intestinal metaplasia [32]. Cui Guoliang et al. applied the method of fortifying the spleen and dispersing stuffiness, transforming phlegm and resolving stasis, and treated PLGC model rats with the Huatan Xiaoyu Formula, finding that it improved the pathomorphological changes of the gastric mucosa in PLGC rats [33].

3.2.4 Stomach Collateral Stasis Pattern

Spleen deficiency and qi stagnation fail to propel blood circulation; blood stagnates internally and forms stasis. Once stasis is formed, it further impairs the functions of the spleen and stomach, creating a vicious cycle that is protracted and difficult to cure. This pattern is characterized by epigastric stabbing pain with a fixed location, tenderness, and a dull, dark complexion. The tongue body is dark red or may have petechiae/ecchymoses; the pulse is wiry and choppy. Under gastroscopy, the gastric mucosa appears granular or nodular, with intramucosal hemorrhagic spots; the mucus is grayish-white or brown; the vascular network is clearly visible, and the vascular lines are dark red. The treatment principle is to regulate qi, activate blood, transform stasis, and relieve pain. The recommended formula is modified Shixiao Powder (Sudden Smile Powder) combined with Danshen Decoction (Salvia Decoction). Suitable Chinese patent medicines include Biling Weitong Granules and Yuanhu Zhitong Granules. Yang Shuangfei et al. found that Danshen Decoction can regulate multiple signaling pathways, exerting anti-inflammatory effects and regulating the cell cycle in the treatment of precancerous lesions of gastric cancer [34].

3.2.5 Stomach Yin Deficiency Pattern

In the prolonged course of PLGC, qi, blood, fluids, and humor are consumed in the later stages, often manifesting as epigastric stuffiness, discomfort, or burning pain, accompanied by hunger with no desire to eat or gastric noisy,

dry mouth, dry stools, emaciation, and reduced food intake. The tongue is red with scanty fluids and little coating; the pulse is thready. Under gastroscopy, the mucosal surface appears rough, the mucosa is thin and brittle with scant secretions, and the rugae show fissure-like changes, becoming thinned or even disappearing, with visible submucosal small vascular networks. The treatment principle is to nourish yin and harmonize the stomach, regulate qi, and relieve pain. The recommended formula is modified Yiguan Jian (Linking Decoction). Suitable Chinese patent medicines include Yangweishu Capsules and Yangyin Qingwei Granules. Fang Jiao et al. used Xinwei Granules, which have the effects of supplementing qi and nourishing yin, resolving toxins and dispersing stasis, to treat PLGC model rats and found that the drug could participate in cell cycle regulation through the Cyclin D1-CDK4/6-P16 pathway, thereby inhibiting the proliferation of PLGC cells [35].

3.3 External Therapies

External therapy in traditional Chinese medicine is a highly distinctive therapeutic approach characterized by strong practicality and high patient acceptance. It can be combined with medication to enhance therapeutic efficacy. Chen Kai et al. found that the combination of Yiqi Huoxue Formula (Qi-Boosting and Blood-Activating Formula) with acupoint application achieved significant efficacy in treating precancerous lesions of gastric cancer, effectively alleviating TCM syndrome scores and reducing the expression of COX-2 and VEGF, thereby helping to lower the risk of carcinogenesis and slow its progression [36]. Pan Rufang discovered that moxibustion could, to a certain extent, improve the degree of gastric mucosal atrophy, intestinal metaplasia, and cellular atypia in PLGC rats [37].

4. Summary

In summary, PLGC is a critical link in the development of gastric cancer, and its prevention and treatment are of great significance in reducing the incidence and mortality of gastric cancer. Currently, Western medicine has made clear progress in elucidating the pathogenesis, diagnostic techniques, and local interventions, but still lacks specific drugs that can reverse the pathological changes. Based on the core pathogenesis that “spleen-stomach weakness is the root, while phlegm, stasis, turbidity, and toxin are the branch,” traditional Chinese medicine, through syndrome differentiation and treatment and comprehensive intervention, has demonstrated unique advantages and potential in improving patients’ clinical symptoms and reversing the pathological and histological changes of the gastric mucosa, reflecting the features of holistic regulation and individualized treatment. However, there are still some shortcomings: (1) There is currently no unified TCM syndrome classification for PLGC. It is necessary to establish unified and standardized syndrome criteria as soon as possible to guide clinicians in diagnosis and treatment. (2) Chinese herbal formulas and patent medicines that have been proven effective still require large-sample, multicenter studies to provide more high-level evidence-based medical evidence. (3) At present, mechanistic studies of Chinese medicinals and formulas are mostly concentrated on animal models. How to better integrate animal models with TCM symptomatology still needs further exploration. (4) Research on TCM external therapies in the treatment of PLGC is relatively scarce and needs to be further explored and continuously developed.

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