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Brief Review on the Causes, Diagnosis and Therapeutic Treatment of Gastritis Disease

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Abstract

Gastritis represent a state of inflammation, irritation, or erosion of the stomach lining which may occur suddenly (acute) or gradually (chronic). Generally there is no universally accepted classification of gastritis and early classification was based mainly on the morphology, but recently pathogenic mechanisms have also been incorporated. The gastric mucosa is continuously exposed to many noxious factors, and Gastric protection aimed mainly to reduce or prevent the chemically induced acute hemorrhagic erosions which is exerted by compounds such as prostaglandins (PG) and SH derivatives without inhibiting acid secretion.

Common causes of gastritis are excessive alcohol consumption or prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin or ibuprofen. It may also develop after major surgery, traumatic injury, burns, or severe infections. Chronic causes are infection with bacteria, primarily *Helicobacter pylori* (HP), chronic bile reflux, stress additionally certain autoimmune disorders can cause gastritis as well. The most common symptom is abdominal upset or pain, indigestion, abdominal bloating, nausea, vomiting and pernicious anemia. The current study here is focusing on the causes, clinical profile, inflammatory, immune response and autoimmune atrophic gastritis in affected individuals. Additional focuses are on different diagnostic tools for *Helicobacter pylori* infection (HP) and current therapeutic treatment.

Keywords: Gastritis; Clinical profile; Inflammatory and immune response; Autoimmune atrophic gastritis; *Helicobacter pylori*; Diagnosis and current medications

Introduction

Overview and pathogenesis

The term "gastritis" refer usually to inflammation, erosive state to the stomach lining tissue which may occur either instantly (acute) or gradually as chronic state [1]. Early classification of the disease was based on tissue morphology which has been changed now with the incorporation of the pathological mechanism. Classification of gastritis was introduced by the Sydney system in 1990, updated in 1995 and included both endoscopic and histological categories [2]. Exposure of the gastric mucosa to noxious factors are continually occur and its resistance to auto digestion by gastric secretion is remarkable and mainly attributed to the presence of mucus gel layer lining the inner surface and acting as tissue protective [3]. Many compounds like prostaglandins (PG) and SH derivatives can induce acute hemorrhagic erosions which can be prevented by the gastro protective mechanism as exerted by the lining mucous. The latter is referred to as complex aqueous mixture of mucin, Electrolytes, Enzymes, bacterial products and scared cells [4]. Its physiological mechanisms are multiple; include formation of thick mucus gel which protects the epithelial surface against noxious factors, irritation or through coating the ingested food for subsequent digestion.

Causes of gastritis

Common causes of gastritis are many like continued intake of alcoholic beverages or long intake of non-steroidal anti-inflammatory drugs (NSAIDS), Aspirin for Rheumatoids and Osteoarthritis patients [5] while Stress, chronic bile reflux, autoimmune disorders and HP infection are causal for chronic gastritis. The symptoms observed her are many like nausea, vomiting, indigestion, burning sensation and abdominal bloating [6]. Blood, stool tests and gastro endoscopy are mostly requested for Diagnosis.

Morphological Patterns

Acute type

Acute gastritis is mostly induced by many agents like certain drugs, bile, Ischemia, viral, fungal, radiation acute stress (shock) and direct trauma. Alcohol consumption does not cause chronic gastritis, but it erode however the mucosal lining of the stomach. Although low doses of alcohol, not the higher one which stimulate hydrochloric acid secretion. Long intake of NSAID may induce an acute erosive gastritis, mostly due to injury and reduced prostaglandin synthesis. Duodenum-gastric bile reflux, long NSAID intake are causal factors for reactive or chemical gastritis (tortosity). Symptoms of the latter are many like cellular irritation of gastric surface associated with vasodilatation, congestion of gastric lamina propria, inflammatory cells and edema [7].

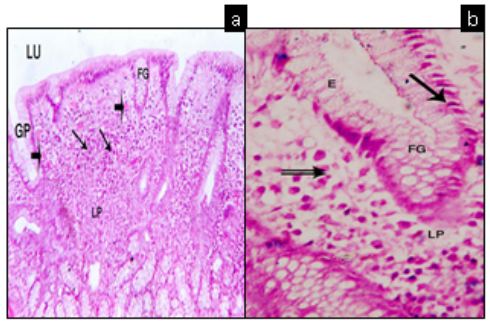

Figure 1: Histological section of human fundic gland of patient suffering from gastritis with anti *H. pylori* IgM positive group showing (a) X100 irregular short fundic gland (FG), wide gastric pit (GP), multiple inflammatory cells (arrows) and blood vessels (double arrows) filling lamina propria (LP), (b) X400 showing irregular simple columnar epithelium (E), small pyknotic nuclei (arrows) of cells lyningfundic gland (FG) and multiple inflammatory cells (double arrows) filling lamina propria (LP)[10].

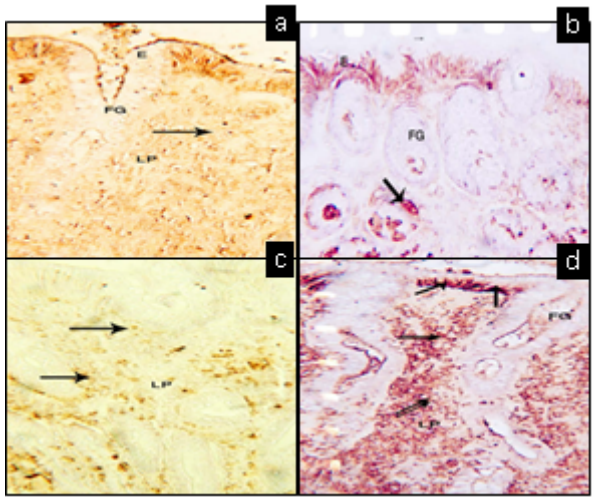

Figure 2: Immunostaining section of Gastritis patients IgM(+) category for (a) nitrotyrosine showing strong positive reaction in the epithelial (E) lining fundic gland (FG) and inflammatory cells (arrows) filling lamina propria (LP), (b) myeloperoxidase showingstrong positive reaction in the surface columnar epithelial cells (E) and other cells (arrows) lining fundic gland (FG) (c) iNOS showing strong positive reaction in the inflammatory cells (arrows) filling lamina propria (LP), (d) DNA fragmentation factor (DFF) showing strong positive reaction in the epithelial (arrows) lining fundic gland (FG) and inflammatory cells (double arrows) fill lamina propria (LP) (X200)[10].

Chronic type

Infiltration of inflammatory cells like plasma cells, lymphocytes represents an inflammatory changes (chronic type) in gastric mucosa, mainly attributed to HP infection along a disturbances in the secretion of pepsinogen enzyme, HCL additionally gastrin and somatostatin hormones. Increased apoptosis, hyper proliferation of the gastric epithelium are also observed during HP infection and is subsequently reduced upon treatment of the infection or eradication of HP [8]. Disturbances between the aggressive and cyto protective factors which maintain the integrity of the gastric mucosa represent a common mechanism of the injury. Inflammatory pattern her include massive increase of oxidative stress (high ROS), pepsinogen, gastrin and nitric acid synthesis (iNOS) with subsequent atrophy and G cells damage. Final apoptosis formation in different cell varieties may be attributed to peroxynitrite formed due to an interaction between NO and reactive oxygen species (ROS) (Figure 1 and 2) [9].

Atrophic Gastritis

Two main categories are known for chronic gastritis, namely atrophic and non-atrophic one [11]. Atrophy her represents the loss of the appropriate glands due to long exposure to HP infection and usually expressed as major risk factor for gastric cancer. Two types of which are recognized, one represented by fibrosis or proliferation of fibro muscular region in the lamina propria while the other represent intestinal metaplasia [12] due to normal mucosa replacement by the of intestinal type.

H. pylori-associated Atrophic Gastritis

Helicobacter pylori (HP) is spiral-shaped, flagellated, Gram-negative bacterium which colonizes the stomach of affected individuals [1,13]. The bacteria induces dyspepsia, peptic ulcers, acute, chronic gastritis, and mainly responsible for gastric-adenocarcinoma, pancreatic cancer [14,15] additionally several autoimmune diseases.

Routs of Transmission

Primary transmission rout is through individual exposure to vomit, (fecal-oral) way additionally contaminated water and food participated with family members [16].

Clinical profile

Infection with HP resulted in symptoms like nausea, vomiting, epigastric pain, hypochlorhydria malaise, fullness and flatulence which may extends to one week regardless any drugs intake or eradication of the bacteria from its location. Chronic gastritis however may appear during persistence of HP infection either asymptomatically or may be manifested as epigastric pain, anorexia additionally nausea and vomiting [17]. Atrophic gastritis may be developed later and characterized by gastric ulcers and adencarcinoma as complications of HP infection. Duodenal ulcer is manifested by burning sensation which may be developed few hours either after meal or at night and disappeared by intake of food.

Relation between HP infection and Oxidative Stress

Oxidative stress is mainly due to increased Free radical synthesis which is usually manifested in many diseases like chronic gastritis, peptic ulcers, gastric cancer [18,19] and HP infection is mainly responsible for such gastric disorders [20]. Specific HP bacterial strains having certain genotype like cag A+/Vac As1 may appear more virulent than the others [20,21]. Inflammatory response by the gastric epithelium her may lead to the production of interleukin-8 (IL-8) and subsequent generation of ROS additionally other cytokines like TNF-α,

interferon ϒ (INF-ϒ), IL-12 and IL-6 (1). Increased level of NO synthesis was also found in certain diseases like duodenal ulcer, gastritis and gastric cancer [22,23]. This is mostly attributed to certain stimuli like bacterial lip polysaccharides, cytokines that are derived from the bacterial wall [24].

The Inflammatory and Immune Response to HP Infection

Pathologically gastric inflammation represents the main mediator her since the immune and inflammatory responses have no effect which allow bacterial persistence for long time. Immune response may be only evident with specific virulence factor which increase gastric inflammation, and stimulate the innate immunity. Local immune effectors in addition may be up regulated by an acquired T helper 1 response [25].

Host response to *H. Pylori*

The immune response towards bacterial pathogens can be divided into an innate and an adaptive response. The innate response towards bacterial infection is generally initial one as non-specific process, which reacts quickly with several bacterial molecules and directed to kill the bacteria. The adaptive immune response however is delayed and antigen-specific leading to the activation of T, B memory cells and is shaped by the innate immune response.

Innate immunity

Recognition of bacterial molecules by the innate immune system is mediated by TLRs (Toll-like receptors) expressed on APCs (antigen-presenting cells) such as monocytes and DCs (dendrite cells). Bacterial contact with monocytes and other APCs leads to the secretion of pro-inflammatory cytokines such as TNF- α (tumor necrosisfactor- α), IL (interleukin)-1β and IL-8. *H. pylori* infection has been shown to be associated with increased levels of these cytokines and acting as local chemo attractants [26,27] and inducing granulocytic infiltration [28]. Accordingly many of the studies on innate immune responses to *H. pylori* in epithelial cells have focused onTLR4, the specific 'pathogen-recognition molecule (PRM) of Gram-negative LPS (lipopolysaccharide).

However, gastric epithelial cell lines were non-responsiveto *H. pylori* LPS, even when relatively high concentrations of this endotoxin were added to the cells [29] and Consistent with this, a TLR4-neutralizing antibody did not block *H. pylori*-induced secretion of the proinflammatory cytokine IL-8 in AGS cells [30].

Humoral response

Individuals colonized with *H. pylori* elicit a strong specific systemic and local antibody response to the infection. Tosi and Czinn reported that binding of IgG to *H. pylori* promoted phagocytosis and killing *in vitro* by polymorph nuclear leucocytes. *H. pylori* strains are susceptible to complement and activate it either via the classical pathway, even in the absence of specific antibodies or by the alternative pathway [31]. Despite this vigorous immune response, *H. pylori* is not eradicated unless an infected individual is treated with a combination of antibiotics, and lifelong chronic infection usually develops. These observations suggest that gastric mucus may be a protective site in which *H. pylori* exist and are relatively inaccessible to specific antibodies or their effector functions.

H. Pylori Vaccine

Whole formalin-inactivated HP is the only vaccine tested in humans [32] and HP0231 prepared vaccine showed no function [33-35]. Collective vaccine from recombinant cag A, vacuolating cytotoxin A and neutrophil activating protein (NAP) represent a well-known trivalent vaccine [36].

Heat shock proteins (Hsp), highly conserved molecules expressed by both bacteria and mammalian species, possess a range of functions, acting as chaperones for cellular proteins and can activate innate immune receptors. Hsp complex (HspC) vaccines, containing Hsp derived from pathogenic bacteria, are immune stimulatory without addition of exogenous adjuvant and can induce immunity against their chaperoned proteins [37]. Expression of HP adhesin (HP0410) was reported in food grade bacteria Lactobacillus acidophilus and was used as oral vaccine in experimental mice. This vaccine has proved to be an effective and promising candidate (vaccine antigen) taken in consideration its low cost of preparation [38].

Autoimmune Atrophic Gastritis

Anti-gastric auto antibodies are detectable in about 30% of *H. pylori* infected patients. Two major in situ binding sites have been found: first at the luminal membrane in antrum, corpus mucosa and secondly at canalicular membranes. The presence of the latter type of autoantibodies is correlated with the histological and clinical parameters of corpus mucosa atrophy. The gastric H+/K(+)-ATPase, which is already known as an auto antigen in classic autoimmune gastritis represents also a major target in atrophic *H. pylori* gastritis [39].

Progressive inflammatory state leading to replacement of parietal cells by atrophic and metaplastic mucosa represents autoimmune gastritis. Autoantibody interaction with parietal cell proton pump and T cells resulted in breakdown of parietal cells which may resulted firstly to decreased HCL levels and lastly a chlorhydria. Its interaction however with intrinsic factor will affect vitamin B_{12} absorption leading to megaloplastic anemia which is collectively termed pernicious anemia [40]. Chronic atrophic gastritis patients additionally develop hyper gastrinemia leading to certain carcinoid tumors. Gastrin is expressed by certain studies as cancer risk biomarker and growth factor for certain malignant tumors in stomach, colon, pancreas and liver cancer. Vaccination with antigastrin for individuals having gastrointestinal cancer represents a simple, low cost tool and promising treatment [41].

Tests for *H. pylori*

Several methods are available to test for *H. pylori* infection.

Breath test (Carbon Isotope-urea Breath Test, or UBT)

Up to 2 weeks before doing the test intake of antibiotics, bismuth medicines such as Pepto-Bismol and proton pump inhibitors (PPIs) must be stopped.

During the test, a special substance like radioactive urea (harmless) is given [42]. If *H. pylori* are present, the bacteria convert the urea into carbon dioxide, which is detected and recorded in exhaled breath after 10 minutes. This test can identify almost all people who have *H. pylori* and to trace the treatment of the infection.

Blood tests

Blood tests are used her to measure antibodies to *H. pylori* and not the current infection where the test can be positive for years even if the infection is cured [43].

Stool test

A stool test can detect traces of *H. pylori* in the faeces in turn it is a diagnostic tool for the infection and confirm the treatment success [44].

Biopsy

Biopsy taken through endoscopy from the stomach lining is the most accurate way to confirm *H. pylori* infection and recommended also to diagnose dyspepsia. Testing for *H. pylori* without endoscopy is done only when the indigestion is new, the person is younger than 55, and there are no other symptoms [45,46]. However Convential PCR and multiple Genetic analysis system (MGAS) could be a potential alternative method for clinical detection and to monitor the effectiveness of HP therapy.

Treatments and Drugs

Depending on the causal factors of gastritis especially acute type due to long intake of non-steroidal anti-inflammatory drugs or alcohol, this can relieved by stopping their use while treatment of the chronic type may require different antibiotics additionally metronidazole.

Gastritis medications

Generally it is recommended to use a combination of antibiotics with metronidazole for 10-14 days [47]. Proton pump inhibitors like omeprazole are also recommended to decrease gastric acid production and facilitate quick healing [48]. Randomized clinical trial for HP gastritis patients using lansoprazole in combination with clarithromycin, amoxicillin, jinghuaweikang gelatin pearl for 10 days followed by additional 14 days using the gelatin pearl alone showed symptomatic improvement dealing with epigastric pain, bloating and belching [49].

Histamine blockers (H-2) are also recommended like ranitidine and cimetidin additionally antacid although side effects of the latter must be taken in consideration.

Natural products as medication for gastritis

Tannins and Flavonoids (Phenolic compounds), mostly found in several medicinal plants have usually certain therapeutic effects. Anti-inflammatory, antioxidant, anti ulcerogenic and wound healing are mostly attributed to these constituents [50].

Antioxidants content of Fresh vegetables and fruits have beneficial effect on GIT mucosa. Curcumin and black seed oil have significant effect on specific mucosal lesions (ulcers) due to their flavonoids content [51]. Many plants like quassin artichoke, quarcetin have inhibitory influence on cytokine mediated inflammatory mechanism, ulcer healing and suppression of NO synthesis (iNOS). The quassionoidisobrucein B (isoB), one of the main constituent of Picrolemmasprucei has proved to provide protective effect against NSAID -induced gastritis. This was attributed to reduction in 1L-1β, TNFα, prostaglandins additionally leukocyte rolling and migration [52].

Licorice extracts have significant effect on HP gastritis and gastric cancer due to its potent ant oxidative, anti-inflammatory, and anti-mutagenic actions. The expressions of COX-2, iNOS, VEGF, and IL-8 were increased after *H. pylori* infection, turned to be significantly decreased with s-lico in a dose-dependent manner [53]. Croton campestris A. St.-Hill., popularly known as "vela me do campo", is a species native from savannah area of Northeast Brazil and used by traditional communities in folk medicine for a variety of health problems, especially detoxification, inflammation and gastritis. CCRE a traditional Brazilian medicine against gastric disorders have antinuclear activity, mostly due to its stimulation of NO synthesis and activation of endogenous prostaglandin production [54].

Discussion and Conclusion

The above article represent a survey on causes, diagnostic tools additionally panel of gastritis treatment. Focus is done on agents inducing acute, chronic types and that in consequence to HP infection. Causes which affect the integrity of gastric mucosa leading to injury and in relation to inflammatory pattern, oxidative stress, hormonal, Enzymes secretion and NO synthesis were also discussed. Role of HP in association with atrophic gastritis, its routes of transmission, symptoms observed in relation to oxidative stress were also reported. Different types of immunity in concern and autoimmune atrophic gastritis were also discussed. Lastly common tests for HP, gastritis medication with special focus on natural products were also outlined.

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