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Chapter 3

Helicobacter Pylori Infection and Its Relevant to Chronic Gastritis

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Additional information is available at the end of the chapter

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1. Introduction

Gastric inflammation is highly complex biochemical protective response to the cellular tissue injury. Chronic gastritis is associated with the inflammatory cellular infiltrate predominantly consisting of lymphocyte and plasma cells in gastric mucosa. Many evidences suggest that Helicobacter pylori (H. pylori) infection and non steroidal anti- inflammatory drug (NSAID) ingestion are major causative factors. Both are highly implicated in the pathogenesis of gastric mucosal oxidative injury in humans.

Chronic gastritis is mainly divided into two main categories namely non-atrophic and atrophic gastritis (*Rugge et al, 2011*). In the gastric mucosa, atrophy is defined as the loss of appropriate glands. Atrophic gastritis, resulting mainly from long standing H. pylori infection and is a major risk factor for the onset of gastric cancer.

Two main types of atrophic gastritis can be recognized, one characterized by the loss of glands, accompanied by fibrosis or fibromuscular proliferation in the lamina propria and the other characterized by the replacement of normal mucosa into an intestinal type of mucosa i.e intestinal metaplasia (Rugge et al, 2007).

Helicobacter pylori is spiral –shaped, flagellated, Gram-negative bacterium. It colonizes the stomach of about 50 percent of the world population, especially in the developing countries (Marshall BJ and Warren, 1983, Bruce and Maaroos, 2008). It is directly implicated in the dyspepsia, acute and chronic gastritis, peptic ulceration, MALT lymphoma and it is an independent risk factor for gastric adenocarcinoma (Atherton, 2006). It may also be a risk factor for pancreatic including cancer (Trikudanathan et al, 2011). H. pylori has been also associated to some extra-gastric diseases including several autoimmune diseases.

2. Geographical distribution of the prevalence of H. pyloriinfection

The prevalence of H. pylori infection varies from country to country with large differences between developed and developing countries (Neunert et al, 2011) The epidemiology of H. pylori infection in developing countries is characterized by a rapid rate of acquisition of the infection such that approximately 80 percent of the population is infected by the age of 20 (Robinson et al, 2007) because the disease is most often acquired in childhood or when young children are present in the household. The prevalence of H. pylori is inversely related to socioeconomic status (Sobala et al, 1991, Blaser and Atherton, 2004).The major variable being the status childhood, the period of highest risk. Attempts to understand the different infection rates in defined groups have focusedon differences in socioeconomic states defined by occupation, family income level and living conditions. Each of these variables measures a different component of the socioeconomic complex.

3. Routs of transmission

H. pylori is a true opportunistic bacterium that will use any method available for gaining access to the human stomach. Gastro-oral (e.g. exposure to vomit) and fecal-oral routs are believed to be the primary means of transmission. The bacterium can also be transmitted through exposure to contaminated food or water. The majority of the data support the notion that transmission is mainly within families. Thus close contact and the level of house hold sanitation appear to be the most important variables. These findings may support the concept that the most likely sources of transmission are person-to-person and /or exposure to a common source of infection.

H. pylori from the Hispanic families living in certain place was examined for relatedness based on the geno types using the cag A, vac A and ice A genes. H. pylori isolated from the children and their mothers had the same genotype and were different from the associated with children's fathers or brothers-in-law (Graham et al, 2004). The high rate of transmission to spouses also suggests that genetic factors are less critical than living conditions for transmission of the bacterium.

4. Relationship between H. pylori infection and associated diseases

AS reported before H. pylori infection causes chronic gastritis, peptic ulcer disease, primary gastric B-cell lymphoma, (indirectly) gastric adenocarcinoma and patients with infection develop gastric damage (Harford et al, 2000, Nomura et al, 2002). Approximately 17 percent of infected patients develop peptic ulcer and one quarter of such patients experience an ulcer complication (Crabtree et al, 1991, Censini et al, 1996). Numerous trials have shown that ulcer relapse is prevented following infection cure (Yamaoka et al, 1998, Yamaoka et al, 1999). Histological and serologic studies have also shown that the infection preceded the ulcer and

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H. pylori infection is now accepted as one of the major causes of peptic ulcers (the other being use of non-steroidal anti-inflammatory drugs) (Higashi et al, 2002).Accordingly development of the disease depends on bacterial, host and environmental factors.

The risk of ulceration is higher with more virulent strains. The best described virulence determinants are expression of active forms of a vacuolating cytotoxine (Vac A)(Crabtree et al, 1995) and possession of a protein secretory apparatus called cag (cytotoxin-associated gene products) that stimulates the host inflammatory response (Ando et al, 2002). Cag+ strains interact more closely with epithelial cells and induce release of pro-inflammatory cytokines, thereby increasing inflammation.

However it is unclear whether it is this or the direct translocation of a bacterial protein (Cag A) into gastric epithelial cells that is the primary cause of the disease, including gastric adenocarcinoma.

Host genetic susceptibility and environmental factors also affect disease risk; for example, smoking is strongly associated with peptic ulceration in H. pylori –infected individuals. H. pylori induced duodenal ulceration arises in people with antral predominant gastritis (Backert et al, 2004, Majumdar et al, 2010). Antral inflammation leads to reduced somatostatin production and, because somatostatin has a negative feedback effect on gastrin production, this results in hypergastrinaemia. Gastrin stimulates enterochromaffin-like cells to release histamine, which acts on parietal cells, resulting in stimulated acid production, increased duodenal acid load and the formation of protective gastric metaplasia in the duodenum. Helicobacter pylori cannot colonize the normal duodenum, but can colonize gastric metaplasia, causing inflammation and ulceration (Majumdar et al, 2010). Hypergastrinemia on the other hand and inconsequence to antral inflammation may leads to an increase of acid production from the acid secreting areas of the stomach in response to food and other stimuli. The resulting increased acid load in the duodenum is one factor encouraging duodenal ulceration. Gastric ulceration occurs on a background of pangastritis often arising at the highly inflamed transitional zone between antrum and corpus, particularly on the lesser curve.

5. Clinical features

Chronic H. pylori –associated gastritis per se is asymptomatic but the initial acquisition of the infection cause acute gastritis with hypochlorhydria which may cause abdominal pain, nausea and vomiting that resolve within a few days (Fischer et al, 2001). Uncomplicated peptic ulcers typically cause epigastric pain and less commonly, nausea, vomiting and weight loss, whereas some ulcers (particularly NSAID ulcers) are asymptomatic. The classically described pain of duodenal ulcer is felt as a growing or burning sensation, often with a relation to meals; occurring 1-3 hours after meals and /or at night and relieved by food. Gastric ulcer pain is instead often precipitated by food. However symptoms are actually very poorly discriminatory for ulceration site and even for whether or not an ulcer is present. Examination usually reveals epigastric tenderness but may be normal.

6. Complications

H. pylori ulcers usually heal and relapse spontaneously but ulcers of any cause, and particularly NSAID –induced ulcers, may cause serious complications.

Acutely bleeding ulcers cause anemia, perforation results in peritonism and gastric outlet obstruction causes persistent vomiting. The discovery of H. pylori therefore has revolutionized the management of peptic ulcers; its eradication heals H. pylori –induced ulcers and prevents their relapse.

7. Dyspepsia in the community

Older patients presenting for the first time and those with alarm symptoms or signs (weight loss, dysphagia, persistent vomiting, gastrointestinal bleeding, unexplained anemia, epigastric mass, previous gastric ulcer or gastric surgery) should be referred for upper gastrointestinal endoscopy and /or other investigations, both to exclude malignancy and to make a positive diagnosis. Other patients (with simple dyspepsia) should normally be treated without endoscopy or specialist referral. These patients should have one of two initial approaches. In populations where H. pylori prevalence is high (≥ 20-25 percent), patients should be tested for H. pylori non-invasively, and given treatment to eradicate H. pylori if positive.

In populations with lower H. pylori prevalence another approach may be followed (inhibitors). In either case, if the first approach fails, the second can be tried (Wirth et al, 1998, Mason et al, 2005, Delaney et al, 2008).

8. Upper gastrointestinal endoscopy

Upper gastrointestinal endoscopy is the investigation of choice in older patients with dyspepsia and those with alarm symptoms because it enables diagnosis of ulceration and of other macroscopic abnormalities such as malignancy and Oesophagitis. Histological examination of gastric mucosal biopsy specimens is useful in confirming the nature of any abnormalities seen, and in identifying whether gastritis is present and its cause. However it is seldom necessary if macroscopic appearances are normal. Treatment with acid –suppressing drugs before endoscopy may heal ulcers, rendering endoscopic findings misleading since proton pump inhibitors, bismuth compounds and antibiotics may cause false-negative H. pylori tests. If possible, acid suppressing agents should be avoided for at least two weeks and preferably 4, bismuth compounds and antibiotics may be avoided for at least 4 weeks before endoscopy.

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9. H. pylori infection and oxidative stress expression

Oxidative stress is associated with many diseases (Yamaoka et al, 2000), including gastric disorders like chronic gastritis, peptic ulcers, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma (Majumdar et al, 2010). These gastric diseases can be the result of infection with Helicobacter pylori, which is believed to be the major etiological age (Chen et al, 2005). Several studies have been carried out focusing bacterial factors in gastric diseases and it has been assumed that H. pylori strains having Cag A+ /VacAs1 genotype are more virulent than other genotypes.

Some studies have reported that Vac As1 strain is usually toxigenic and tends to be CagA+ (Moss et al, 1992).

H. pylori infection induces an inflammatory response that is also oxidative. The gastric epithelium and the bacteria induce production of interleukin-8 (IL-8) that contributes to the generation of great amounts of toxic reactive oxygen species (ROS), with marked infiltration of inflammatory cells and can elicit induction of interleukin-1β (IL-1β), interleukin -6 (IL-6), IL-8, IL-12, tumor necrosis factor-α (TNF-α) and interferon-γ (INF-γ) (Marshall et al, 1985). The inflammatory response induced during H. pylori infection does not appear to confer protective immunity and the resulting oxidative burst caused by phagocytic cells can damage gastric tissues (Graham et al, 2004). Increased pathogen- inducible nitric oxide synthase (iNos) has also been observed in the gastric mucosa of the patients with duodenal ulcer (2010), gastric cancer (Mason et al, 2005), gastritis (Delaney et al, 2008) caused by H. pylori infection. iNos is induced by a variety of stimuli, including bacterial Lipopolysaccharide, cytokines and products from the bacterial wall (Janssen et al, 1992) and its expression contributes to oxidative stress.

Another oxidative enzyme induced by H. pylori in gastric disease is Nox1 (NADH oxidase 1) (Blaser and Atherton, 2004). It constitutively produces both superoxide anion and Hydrogen peroxide (H_20_2). Increased expression of Nox1 mRNA moderately increases superoxide generation, which leads to a reduction in aconitase activity, making Nox1 a good marker of oxidative stress (Tandon et al, 2004).H. pylori also induces ROS production by gastric epithelial cels, contributing to increased damage in the mucosa (Naito and Yoshikawa, 2002) and H. pylori itself generates great amounts of superoxide anions to inhibit bactericidal action of nitric oxide (N0) produced by inflammatory cells (Atherton, 1997).

Another source of ROS that contributes to oxidative stress is the H202 generated by TNF-α and other cytokines that are essential for their activity (Atherton et al, 1995) since H202 in the presence of ferrous or cuperous ions can catalyzes the generation of the highly reactive hydroxyl radical by Fenton reaction (Noach et al, 1994), an increase in H202 concentration induced by cytokines makes also TNF-α expression a good oxidative stress marker.

TNF-α is produced by a wide variety of cell types and it is positively regulated under stress and pathological conditions (Meyer et al, 2000). Protection of cells against ROS is accomplished through the activation of oxygen-scavenging enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase (CAT).

However it is not well known how H. pylori bacteria products and inflammation affect the ability of gastric cells to protect themselves from damage caused by ROS. The virulence of the strain acts primarily as an accelerator in the disease process and not as a predictor of outcome.

10. The immune response to H. pylori

H. pylori is an active stimulator of both the innate and acquired immune responses. Local innate recognition of H. pylori by epithelial cells is thought to be an important disease determinant. There are also strong local and systemic antibody and cell-mediated immune response

11. The innate immune response

H. pylori colonization of the gastric mucosa triggers innate host defense mechanism thus stimulating the expression of pro-inflammatory and anti-bacterial factors by gastric epithelial cells (Antos et al, 2001). The first line of defence results in gastritis and H. pylori also stimulates innate immune responses from these infiltrating cells (Kawahara et al, 2001) which may subsequently influence bacterial colonization density (Arnold et al, 2001), the inflammation level and also the generation of adaptive response may represent a central determinant of disease severity and participation is thought to be a major mediator in gastric carcinogenesis.

12. Antimicrobial peptides

Secreted antimicrobial peptides, including defensins are produced as part of the innate immune response to H. pylori. Elevated levels of human β defensin (hBD2) and the neutrophil-derived alpha defensins 1,2 and 3 are present in the gastric juice of H. pylori –infected patients (Nagata et al, 1998) and increased expression of hBD2 (Beutler and Cerami, 1986),hBD3 (Meneghini, 1998), adrenomedullin (Jung et al, 1997), angiogenin (George et al, 2003) and the human cationic antimicrobial peptide 18 (Gobert et al, 2004) LL-37 (Harris et al, 1998) has been shown in infected human gastric epithelial cells.

13. The acquired immune response

H. pylori infection provokes a vigorous humoral and cellular immune response in humans, but the organism is rarely eliminated from the gastric mucosa and infection persists lifelong in the absence of treatment (Blaser and Atherton, 2004). One possibility is

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that H. pylori itself influences the immune response to avoid its own clearance by the host and to down-regulate excessive host damage thus promoting a relatively peaceful co-existence. However, there is good evidence that the acquired immune response itself contributes to gastro-duodenal disease processes (Zevering et al, 1999). Mouse models have shown that the cellular immune response is a central regulator of H. pylori-induced gastric inflammation and pathology. Mice deficient in IL-10 mount a vigorous inflammatory response to H. pylori, successfully and rapidly clear H. pylori infections (Chen et al, 2001).

14. Humoral immunity

H. pylori stimulates the production of mucosal and systemic IgA and IgG s, but the effect of antibody upon bacterial colonization remains controveial. One report showed that the intragastric administration of specific monoclonal IgA mediated protection against H.fellis infection in mice (George et al, 2003). In contrast, others have shown that specific IgA and IgG in mice actually promote bacterial colonization and reinhibit protective immune mechanisms (Akhiani et al, 2004, Akhiani et al, 2005). H. pylori is susceptible to the compliment-mediated bactericidal activity of serum (Gonzalez-Valencia et al, 1996) but it is possible to successfully immunize B-cell deficient mice (Ermak et al, 1998, Sutton et al, 2000), indicating that antibodies are not essential for protection. The B-cell response plays an important role in pathogenesis through participating in an H. pylori –precipitated autoimmune process (D'Elios et al, 2004). In this, antibodies cross-react with host antigens such as those on gastric epithelial cells and the parietal cell H+,K+_ATPase(Amedei et al, 2003), potentially inducing local- inflammation and damage.

15. The T-cell response

In humans, the T-cell response to H. pylori is dominated (Fan et al, 1994, Bamford et al, 1998). Th1 cells produce IFNγ and this type of response is associated with pro-inflammatory cytokine expression, for example TNFα, IL-12 and IL-18. When macrophages are activated in the presence of such type I cytokines, the resulting " angry " macrophages secrete pro-inflammatory factors and have enhanced bactericidal activity compared to those activated in the presence of Th2 cytokines (Ma et al, 2003). The number of IFNγ-secreting cells in the infected human gastric mucosa correlates with the severity of gastritis (Lehmann et al, 2002). IFNγ itself appears to be a key mediator, as infusion into mice, even in the absence of H. pylori infection, induces pre-cancerous gastric atrophy, metaplasia and dysplasia (GeaCui, 2003). Some strains of mice, such as C57BL/6, which mount a strong Th1 response to H. pylori, have more severe gastritis but reduced colonization densities (Gerhart et al, 2000)

16. Tests for H. pylori

16.1. Tests not requiring endoscopy

Serology:serological tests involve detection of IgG antibodies against H. pylori and the best are very accurate. However, accuracy depends critically on the precise serological test used. Serology may remain positive for years after successful eradication of H. pylori and therefore is not used for checking the treatment success, it is cheap (Majumdar et al, 2010)

Urea breath test (UBT): the UBT is a simple, non invasive test based on H. pylori urease. It is particularly useful for checking the success of treatment. It is also more accurate than serology and often used as a first-line diagnostic test in places where it is readily available. It must be performed at least 4 weeks after any bismuth compounds, antibiotics or proton pump inhibitors have been stopped. If not, false-negative results are common. It is inexpensive and readily available to general practioners in most countries.

Stool antigen test:It is more developed as alternative to the urea breath test (Gisbert et al, 2006). Like the latter it assesses active infection and so can be used for assessing treatment success since it is less expensive than the UBT.

16.2. Test requiring endoscopy

Biopsy UREASE TEST: The biopsy is placed in a urea solution or gel with a PH indicator. When H. pylori is present, the urea is hydrolysed by its urease, resulting in a color change. Some positive results may be available within minutes, although initially negative tests must be kept for 24 hours to avoid occasional false-negative results. Blood in the upper GIT may also sometimes cause a false-negative test. The biopsy urease test is cheap and widely available

Histology: H. pylori infection can be diagnosed accurately by histology if special stains are used. The distribution of gastritis may give information on disease risk if biopsies are taken from antrum and corpus (Figure 1)

Histology can also give further information, for example on whether gastric atrophy or intestinal metaplasia- markers of increased risk of gastric adenocarcinoma- are present. Histology is relatively expensive, particularly if special stains are used (Figure 2)

Culture: Endoscopic mucosal biopsy specimens can be cultured for H. pylori. Although some studies referred to it as being not useful as a purely diagnostic test as H. pylori is not straightforward to grow, and culture is often falsely negative. However success rates are high in others, isolates obtained from biopsy of certain individuals having positive IgM serologically were used for induction of gastritis in experimental rats (Elseweidy et al, 2010).

The serum concentrations of pepsinogen 1 and 11 (Pg1, Pg11), gastrin (G17) and HP antibodies of IgG class have been used to assess the risk of atrophic gastritis and to differentiate between HP-related and non HP- related gastritis (Elseweidy et al, 2010).

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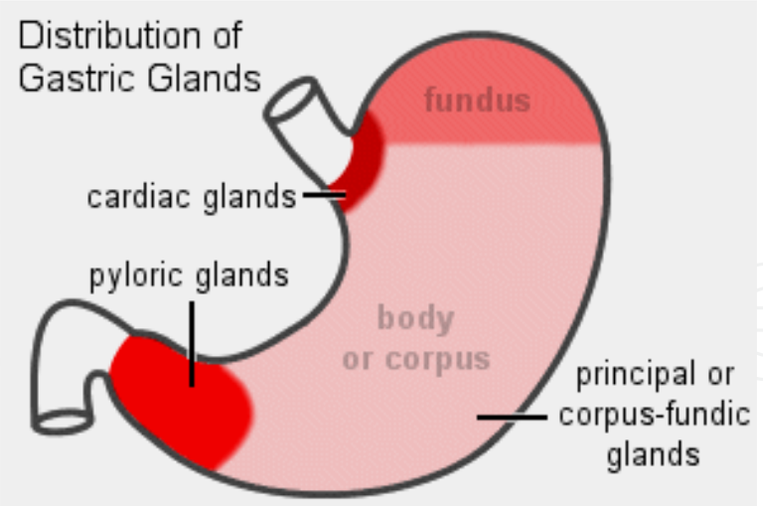

Figure 1. Zones of antrum and corpus-fudic glands of the stomach

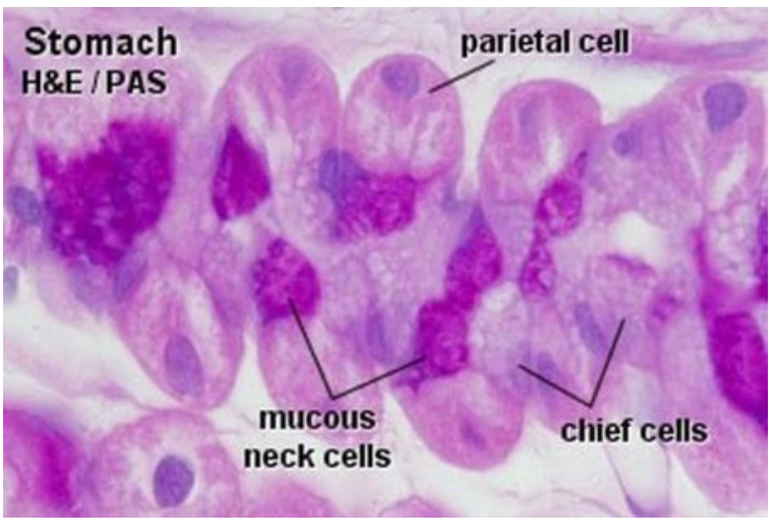

Figure 2. Distribution of parietal and chief cells of normal tissues (H&E stain)

To verify such concept, certain clinical study was designed mainly to identify the pattern of chronic gastritis and the potential effect of HP infection. Certain biomarkers, histological and immunochemical tests were used for assessment.

Fifty eight patients, clinically diagnosed as having chronic gastritis (median age 45 y; range 38-52 y, 9 females, 49 males) were participated in the present study. They were categorized into two groups.

The first one 31 percent demonstrated positive reaction to IgM- Ab of HP (≥ 40 u/ml) and the second group 69 percent demonstrated negative reaction. All the patients had signs of chronic gastritis which vary between them like abdominal pain, heartburn, vomiting or nausea, flatulence or chronic dyspepsia, epigastric pain or nausea, constipation and anorexia

(Robinson et al, 2007). Fasting blood samples were collected from the patients before their direction to endoscopy procedure of the upper GIT with gastric biopsies. Blood samples were directed for the determination of serum gastrin (G-17), Pepsinogens (Pg1,Pg11), Prostaglandin (PGE2) and Interleukin 6(IL -6).Immunohistochemistry technique was also done in antral biopsy to demonstrate the expression of INOS, Nitrotyrosin, DNA fragmentation, myeloperoxidase and histopathological examination (Elseweidy et al, 2010)(Figures 3,4).

Serum gastrin, Pg1, 11, PGE2, IL-6 demonstrated significant increase in gastritis patients as compared to normal individuals. Sector of HP patients having +veIgM showed significant increase of Pg1, 11 and slight increase of IL-6 as compared to negative sector

Immunostaining tests in antral biopsy showed strong positive reaction for the above mentioned markers as compared to IgM negative group which demonstrated mild positive reactions (Figure 5)The study concluded that gastritis patients who express positive IgM for HP infection showed higher gastrinaemia and more pronounced atrophic, inflammatory and apoptotic damage than those not expressing IgM- Ab(Elseweidy et al, 2010).

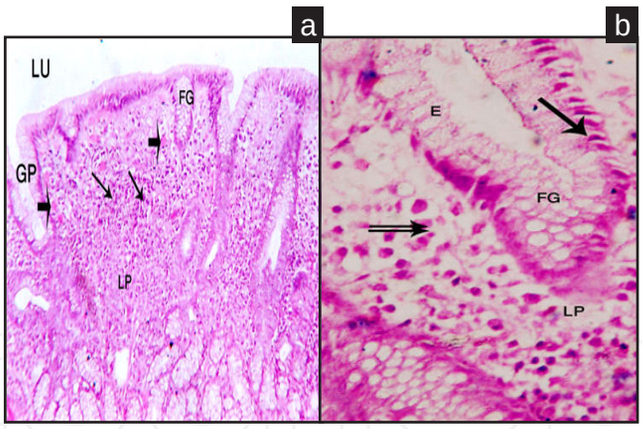

Figure 3. Histological section of human fundic gland of patient suffering from gastritis with anti H. pylori IgM positive group showing (a) x100 irregular short fundic gland (FG), wide gastric pit (GP), multiple inflammatory cells (arrows) and blood vessels (double arrows) filling lamina propria (LP), (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)(Elseweidy et al, 2010).

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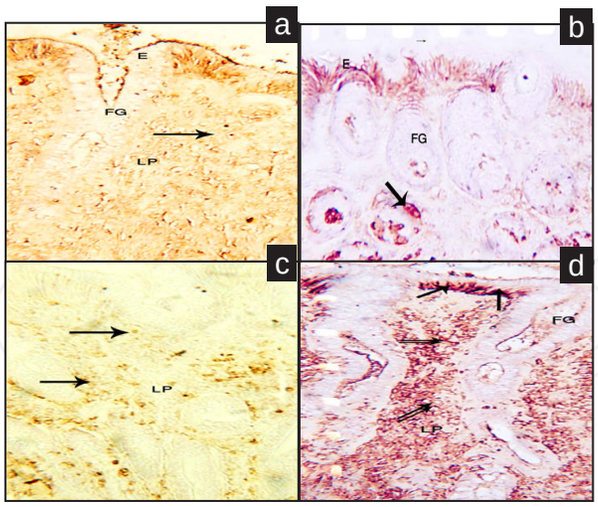

Figure 4. Immunostaining section of Gastritis patients IgM(+) category for (a) nitrotyrosine showing strong positive reaction in the epithelial (E) lining fundic gland (FG) and inflammatory cells (arrows) filling lamina propria (LP), (b) myeloperoxidase showing strong positive reaction in the surface columnar epithelial cells (E) and other cells (arrows) lining fundic gland (FG) (c) iNOS showing strong positive reaction in the inflammatory cells rows) 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)(Elseweidy et al, 2010).

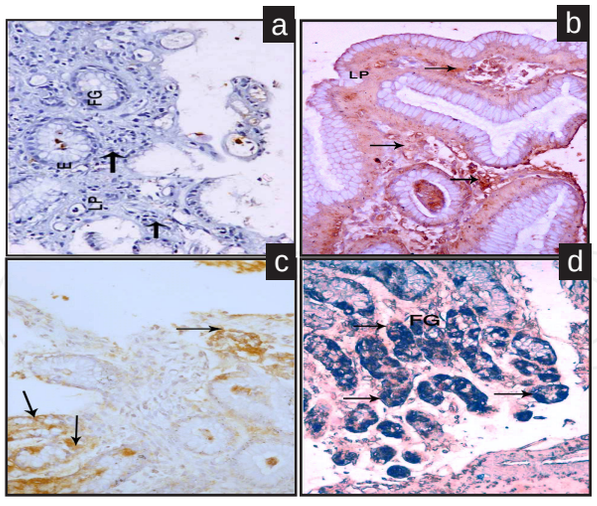

Figure 5. Immunostaining section of human fundic gland from gastritis patients, with anti-H. pylori IgM(-) showing for (a) nitrotyrosine negative reaction in the epithelial (E) lining fundic gland (FG) and inflammatory cells (arrows) filling lamina propria (LP), (b) myeloperoxidase showing strong positive reaction in the inflammatory cells (arrows) infiltrating lamina propria (LP) (c) iNOS showing moderate positive reaction in the cells of the fundic gland (arrows), (d) DNA fragmentation factor (DFF) showing mild positive reaction in the epithelial cell (arrows) lining fundic gland (FG) (x20) (Elseweidy et al, 2010).

17. Eradication of Helicobacter pylori

First –line treatment is usually a 1 or 2-week triple combination therapy comprising twice-daily use of omeprazole, clarithromycin plus metronidazole or amoxicillin. It is successful in 80-90 percent of cases (Marshall et al, 1985). The most common reasons for failure are antibiotic resistance and poor compliance with treatment. Resistance to clarithromycin is increasing and is a crucial determining factor in treatment success. Patients with previous exposure to clarithromycin should not receive this drug for H. pylori treatment unless antibiotic susceptibility testing shows that they have a sensitive strain. Metronidazole resistance is also very common, in particular amongst those having previous exposure to the drug.

So new research has been developed in natural products with anti HP activity.

When Nigella sativa L. (Ranunculaceae) seeds were given to patients with dyspeptic symptoms and found positive for HP infection in a dose of 2g/d along with 40 mg/d omeprazole, it possessed clinically useful anti HP activity (O'Mahony et al, 2005). Solamumlyratum-Thunp (SLE, Solanaceae) showed a moderate ability in inhibiting growth of HP and its association with host cells (Enomoto et al, 2010)

Curcumin from turmeric (Curcuma longa, longa, Zingiberaceae) has been lastly shown to arrest HP growth. Its potential was highly effective in eradication of HP from infected mice and to restore gastric damage, induced by chemicals like iodoacetamide(Elseweidy et al, 2008, Chowdhury and Mukhopadhyay, 2009). Crude essential oil obtained from the dried aerial parts of Thymus Caramanicusjalas (Lamiaceae) at a concentration of 0.33 ul/ml was tested in vitro against clinical isolates and proved to be highly effective.

Aqueous extract of Glucyrrhiza –globra L (Fabaceae) 1mg /ml significantly inhibited the adhesion of HP to human stomach tissue. The effect was related to the polysaccarIdes isolated from the extract (Eftekhar et al, 2009)

18. Prospects for future vaccines

The prevalence of antibiotic resistance amongst H. pylori isolates is increasing, and there are reports of over 50 percent of isolates being resistant to metronidazole in parts of Asia and Africa (Lwai-Lume et al, 2005, Kim et al, 2006).Such antibiotic resistance is a problem for many pathogenic bacterial infections, and large scale control of such infections is probably best achieved through vaccination programmes. Although vaccination appears the logical approach to control H. pylori, however vaccine research has not been straightforward and may need extensive efforts to achieve significant results.

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