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Review Article

Helicobacter Pylori – A Review

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Abstract: Helicobacter pylori, originally classified under the genus Campylobacter, are a gastric, spiral or coccoid Gram-negative microaerophilic bacillus. Helicobacter pylori were first cultured invitro, and found to be associated with gastritis and peptic ulcers, by Marshall and Warren in 1982. Human gastric spiral organisms were discovered in 1906, in vomit from a patient with gastric carcinoma and were first described in human gastric mucosa in 1938, in a series of post-mortem specimens. The discovery of H. pylori offered the etiologic agent of the initializing event of the inflammatory cascade. Later on, it was confirmed that the development of gastric cancer takes over several decades sequentially starting with the acquisition of H. pylori infection and the development of chronic active gastritis. Over the time, the development of glandular atrophy and intestinal metaplasia takes place in a subset of patients. Finally gastric cancer arises. In 1994, the International agency for Research on Cancer monograph committee classified H. pylori as class I carcinogen to humans.
Keywords: Helicobacter pylori, Atrophic Gastritis, Intestinal Metaplasia, Giemsa, Histopathology, Gastric Ulcer, Gastric Carcinoma.

INTRODUCTION

Helicobacter pylorus is part of a genus of bacteria that have adapted to the ecological niche provided by gastric mucus which is lethal to most bacteria. In 1982, Warren and Marshall provided the first insight into an important pathogenic factor in peptic ulcer disease (PUD). They isolated a spiral, urease-producing organism nestled in the narrow interface between the gastric epithelial cell surface and overlying mucus gel [1]. H. pylori are the most important etiological association with chronic gastritis is chronic infection. In addition to chronic gastritis, peptic ulcer disease and gastric carcinoma were a strong causal association with H. pylori has been established, it has a definitive etiological role in gastric MALT (mucosa-associated lymphoid tissue) lymphoma [2]. H. pylori infections occur worldwide; the age at which a patient becomes infected reflects local hygiene. Numerous validated methods to diagnose patients with H. pylori infection are in use. These methods can be divided into invasive and non-invasive diagnostic tests. The invasive tests include endoscopy followed by gastric biopsy and histological demonstration of organisms, biopsy with direct detection of urease activity in the tissue specimen and biopsy with the culture of the H. pylori organism. Histological demonstration of H. pylori by the modified Giemsa is the method of choice because it is sensitive, cheap, easy to perform, and reproducible [3].

ENDOSCOPIC APPEARANCES

In acute gastritis, mucosa has a hemorrhagic appearance due to diffuse oozing from many superficial areas of ulceration. Peptic ulcers are often deep and measure > 0.5 in diameter, penetrate muscularis mucosa. Gastric peptic ulcers typically develop along the lesser curvature, at the antral-corpus junction. Those that measure >3cm in diameter are referred to as giant gastric ulcers. Benign ulcers typically appear as round to oval, sharply demarcated, punched out lesions with perpendicular walls. Surrounding mucosa is congested, edematous and overhangs the ulcer margin, giving it a flask shaped appearance. The lip should not appear rolled or heaped up. Ulcerated carcinomas are shallow irregular bowl-shaped lesions with rolled or heaped up sloping borders and a necrotic base [4]. Well developed atrophic gastritis produces a thin, smooth mucosa with the undue prominence of submucosal vessels.

Hyperplastic polyps tend to occur against the background of chronic gastritis, are seen randomly distributed in the stomach, appear small, sessile, single or multiple, with a smooth or lobulated contour. Severe reflux esophagitis gives a markedly hyperemic appearance to the mucosa.

STRUCTURE

The organisms are seen as slender, curved spirals in the superficial mucus layer, where they tend to be attached to the epithelium at the site of intercellular junctions. Occasionally, H pylori can be present in the stomach as coccoid forms, which appear solid, round, basophilic, dot-like structures on routine histology. Coccoid forms invariably coexist with spiral forms. Ultra structurally, coccoid forms are horse shoe-shaped with ends of both arms are joined by a thin membranous structure. Other intragastric organisms rarely identified are Helicobacter heilmannii, which have a tight, corkscrew appearance on Giemsa stain [5]. Histopathology is an accurate and sensitive method for detection of H. pylori, with organisms identified on H&E stain in more than 80% cases using an oil immersion lens. Other stains, including modified Giemsa stain, Warthin-Starry silver stain, Giemenez, improved Toluidine blue stain, Brown-Hopps stain has also been used to identify these organisms. In a study conducted by Lin SK et al, 23 out of 24 subjects showed H pylori on histology.

PREVALENCE

Helicobacter pylorus is one of the most common pathogens worldwide. It develops and forms colonies in gastric mucosa of about 60% of the world's population, causes gastritis and peptic ulcer and is strongly associated with gastric adenocarcinoma and lymphoma. Childhood represents the major period of acquisition of infection in the third world, but infection is rare in children in the developed world [6]. In a review of epidemiologic studies published on H pylori occurrence and transmission between April'06 and March'07, it was found that prevalence increased with age and was higher in non-white populations; both phenomena being independent of gender. The risk factors for infections, i.e. crowding, type of drinking water, lack of toilet facilities during childhood, lower family income, lower educational level and previous gastrointestinal endoscopy, were observed [7]. The study conducted by Shimizu N *et al.;* provides the epidemiological evidence for a significantly greater prevalence of H pylori infection in developing countries than in developed ones. In various studies conducted by Graham DY *et al.;* and Megraud F *et al.;* it was found that prevalence of H pylori infection varies among different races and among populations of different countries [8, 9]. In a study conducted by Matsuhisa TM *et al.;* the prevalence of H pylori infection in various age groups and various populations was studied. It was found that Chinese, Thai, Vietnamese and Japanese patient populations had a prevalence rate of 62.3%, 82.6%, 45.7%, and 68.6% respectively [10].

TRANSMISSION

Routes of infection for H pylori transmission are oral-oral, fecal-oral route or iatrogenic spread with inadvertent use of unsterilized pH probes and endoscopes and vectorial spread by flies [6]. It has been found that intrafamilial transmission, especially via infected mothers, plays a major role in the spread of H.pylori infection [11-14]. In another study conducted by Yang YJ, this finding was supported by a high prevalence rate of H.pylori infection i.e. >20%, as compared to 8% in the age matched children in general population. It was concluded in the same study that, children living with H.pylori infected mothers have a 4.6 fold higher risk of acquiring H pylori infection as compared with those living with non-infected mothers [15]. Two sero-epidemiologic studies, one from a developed country (Sweden) and one from an underdeveloped country (Benin/Africa), demonstrated a strong familial clustering of H.pylori infection [16, 17]. That water may have a role in the transmission of H pylori in developing countries, as pointed by a study conducted by Queralt *et al.;* in more feces polluted waters, suggesting that water may be a vector of H pylori in its faeco-oral route [18]. There is no documented predominant route of transmission. The only significant reservoir of infection for helicobacter appears to be humans themselves.

COLONISATION AND ADHERENCE

H.pylori colonizes the gastric mucosa (particularly the antrum and cardia) in a variety of ways; free in mucus, adherent to the mucosal surface, intracellularly and intracellularly. The location between the cells provide protection from the acid gastric contents, but permits enzymes (urease and catalase) produced by Helicobacter to damage the gastric epithelium. Cases with intracellular colonisation show the greatest degree of epithelial damage, which include disintegration and loss of apical mucous with formation of epithelial pits, less frequently erosions and ulcerations [19]. H pylorus colonizes the stomach by producing urease and Gastric acid inhibitory protein. After traversing the mucus layer with its polar flagella, adhesion to the gastric epithelium occurs by tissue-specific proteins 'adhesins'. Several of the H.pylori Hop proteins (outer membrane proteins) have been classified as adherence and pathogenic factors, including BabA, SabA, OipA, AlpA and AlpB [19, 20]. Ultimately, it adapts to the host environment with the help of heat-shock proteins [21, 22].

PATHOGENESIS

The clinical outcome of H pylori infection is determined by a complex scenario of interactions between the bacterium and the host. Straight destruction to the host occurs by the effect of urease and other enzymes produced by the bacteria. Some strains produce a soluble factor – vacuolating cytotoxin – encoded by the vacA gene which is present in all strains. Vacuolating activity is associated with the protein encoded by cytotoxin–associated geneA (cagA) [20]. Infection with cagA gene positive strains is associated with greater number of organisms in the tissue, more severe epithelial damage, greater acute and chronic inflammation, higher likelihood of peptic ulceration and increased risk for gastric cancer. DNA region which is a marker of cytotoxicity has been identified and is called "Pathogenicity Island", which encodes proteins responsible for cytotoxicity, signal transduction and induction of cytokines.

LESIONS CAUSED BY H.PYLORI GASTRITIS

Gastritis is an inflammatory condition of the gastric mucosa characterized by elementary lesions whose extent and distribution are related to their etiology and host responses and that may include structural alterations of the glandular compartment as well. The phenotypes of gastritis are described according to the presence or absence of atrophy.

Thus, classified as

Non-atrophic gastritis
Atrophic gastritis

Non-atrophic gastritis been further divided into:

Antral-predominant non-atrophic gastritis
Nonatrophic pangastritis

Atrophic gastritis includes:

Atrophic chronic gastritis
Atrophic pangastritis
Multifocal atrophic gastritis

Atrophic chronic gastritis is further sub-classified as:

Antrum-restricted atrophic gastritis

Corpus-restricted or Corpus predominant atrophic gastritis

Chronic gastritis has been divided into 2 types having similar histologic features but a presumed different pathogenesis.

Type A or Immune gastritis
Type B or non-immune gastritis

H. pylori infections begin as acute gastritis with a marked neutrophilic infiltrate in the mucous neck region of gastric pits but the infiltrate does not affect the superficial epithelium where the organisms are located. Neutrophils, eosinophils, basophils, macrophages, monocytes, plasma cells and mast cells infiltrate the mucosa. The term 'active gastritis' refers to the persistence of enzymatically active neutrophils in a gastric mucosa that also contains chronic inflammation and reflects the continuing destructive activity of neutrophils on the gastric epithelium. Acute gastritis quickly evolves into chronic inflammation. In early stages, chronic inflammation remains confined to the superficial gastric mucosa, often along lesser curvature in the antrum. Plasmacytosis then extends for variable distances into a glandular compartment and then inflammation becomes confluent.

Antral-predominant chronic gastritis is the most common expression of H pylori gastritis, which is characterized endoscopically by a moderate to severely inflamed antrum and a normal to mildly inflamed corpus with either normal or increased acid secretion or absence of atrophy. The corresponding histological features are increased in cellularity of lamina propria due to mononuclear inflammatory cells. Plasma cells and lymphocytes with occasional formation of follicles predominate, but eosinophils and neutrophils may also be present. In a study conducted by Thijs JC *et al.;* it was concluded that all antral-biopsy based tests are accurate for the diagnosis of helicobacter pylori infection [23]. When the inflammatory cell infiltrate is restricted to the foveolar region and unaccompanied by glandular atrophy, the condition is designated as chronic superficial gastritis. In North America and Western Europe, most individuals with H pylori infection have an active superficial gastritis, largely confined to the antrum. This type of gastritis may result in duodenal ulcer formation, probably as a result of increased basal acid output and a heightened parietal cell response to stimulation [24].

Non-atrophic pangastritis is seen in some subjects infected with H.pylori, as marked inflammation distributed throughout the stomach, particularly frequent in poorly sanitized areas with high levels of H pylori prevalence. Pangastritis is widely believed to be the background on which atrophy eventually develops. Helicobacter pylorus favorably infects the antrum but has the ability to infect any part of the gastric mucosa. When antral H pylori are present, they are often also present in the cardia; the density of organisms can be similar in both regions. Treatment of gastric symptoms with proton pump inhibitors alters the pattern of H. pylori infection with the migration of the organisms from antrum to the fundus and a decrease in activity of antral gastritis.

Lymphoid follicles appear in the lamina propria in H.pylori induced gastritis, the lesion termed

as follicular gastritis. Lymphoid aggregates constitute a significant histopathological marker of helicobacter-induced chronic gastritis. Lymphoid tissue hyperplasia is a specific immunological response to H. pylori infection. The study by Chen XY *et al.;* has shown a significant decrease in lymphoid follicles and aggregates following the eradication of H. pylori infection. They have confirmed a significant correlation between lymphoid follicles and aggregates and the severity and activity of inflammation in the gastric mucosa. Lymphoid follicles and aggregates were maximal in the infected antral mucosa in patients with severe chronic active gastritis, which in turn positively correlates with the density of colonization of the gastric mucosa by H. pylori.

Two types of metaplastic changes can occur in chronic gastritis, often in combination:

- Pyloric metaplasia of the fundic mucosa
- Intestinal metaplasia
- In pyloric metaplasia, replacement of fundic type glands by mucus secreting glands occurs. This is a gradual process so that the fundic-pyloric junction moves proximally towards the cardia.

Intestinal metaplasia means the progressive substitution of the gastric mucosa by epithelium having the light and electron microscopic features of intestinal epithelium of either small or large bowel type. The metaplastic epithelium includes eosinophilic enterocytes with a well-developed brush border and goblet cells secreting acid mucin. The only major difference from small bowel mucosa is the usual, poor development of villi [25].

Intestinal metaplasia has been divided into:

- Complete (Type I) and
- Incomplete (Type II) type

Predominant mucin present in complete intestinal metaplasia is sialomucin. The incomplete form contains small amounts of sulfomucins and/or neutral mucins, in addition. The predominance of neutral mucins is seen in Type IIA and Sulfomucins are predominantly seen in Type IIB. Incomplete metaplasia, gastric mucosa changes to a small bowel epithelium type, with the development of villi and crypts in the most advanced cases. In incomplete metaplasia, absorptive cells are absent, whereas columnar cells with the appearance of gastric foveolar cells are retained.

The relationship between intestinal metaplasia of the stomach and H. pylori is of interest. H. pylori is usually absent in foci of type I intestinal metaplasia but often present in Type II foci. Type IIB intestinal metaplasia is said to show a closer association with the intestinal type of gastric carcinoma. When the inflammation in the mucosa is more extensive and accompanied by glandular atrophy, the condition is termed chronic atrophic gastritis. This is further classified as mild, moderate or severe by roughly estimating the thickness of the glandular portion in relation to the thickness of the whole mucosa. This is manifested by an increase in the distance between the individual glands. If thinning of the mucosa is seen in absence of inflammatory changes, the condition is designated Gastric atrophy.

MULTIFOCAL ATROPHIC GASTRITIS (MAG)

Multifocal atrophic gastritis (MAG) is the most common form of chronic atrophic gastritis and it too associates with the presence of H. pylori infections. The H. pylori infections are highly prevalent in MAG with up to 100% of cases being positive. The atrophic foci appear first on the lesser curvature on both sides of the antral corporal junction. Histologically, MAG consists of superficial gastritis, regenerative epithelial changes, glandular loss, intestinal metaplasia, and erosions4. Severe inflammation may be seen in the oxyntic mucosa, and acid secretion may be reduced, suggesting a more advanced disease [26]. Lesions progress in severity and extension. H. pylori are important in the progression to atrophic gastritis [4].

The study by Zhang C *et al.;* indicates that H. pylorus appears to be the most important risk factor for the development of glandular atrophy and intestinal metaplasia. Progression of atrophy and intestinal metaplasia seem to have a key role in the distribution of H. pylori colonization [27]. In the same context, Kato *et al.;* concluded that H.pylori induced inflammation and gastritis could increase the risk of antral atrophy in children [28]. Hypochlorhydria in atrophic gastric mucosa and intestinal metaplasia in gastric epithelium and glandular tissue both contribute an unfavourable environment for the growth of H. pylori and thereby responsible for the absence of H. pylori from such sites [29].

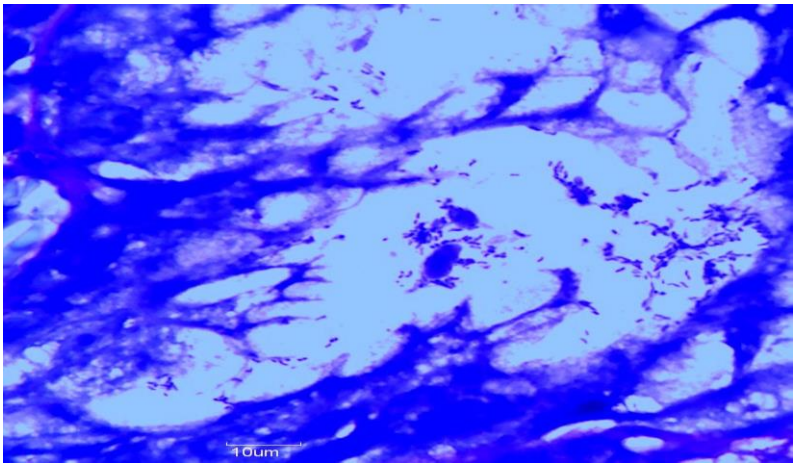

Fig-1: Photomicrograph showing severe colonization of H. pylori organisms – numerous, similar forms seen adjacent and attached to glandular epithelium (Giemsa, 1000X)

GASTRIC ULCER

About 95% of patients with duodenal ulcer and 70-93% of patients with gastric ulcer have H. pylori infection. The mucosa, weakened by H. pylori infection, becomes susceptible to acid attack, especially in the face of increased gastric acid production, explaining the relationship between H. pylori infection and peptic ulcer disease [4]. In a prospective study conducted by Kenichiro M *et al.;* to assess the risk of development of gastric ulcers in patients with H pylori infection, it was found that gastric ulcers developed in 8 (15%) out of 52 patients with H pylori infection as compared to none in the non-infected group, when they were kept under a 52 months follow-up, the difference being statistically significant ($p < 0.05$). The development and location of gastric ulcers were correlated to the development or progression of mucosal atrophy. Gastric ulcers developed in 8 (38%) out of 21 patients with mucosal atrophy but none developed in 31 patients without atrophy. Thus it was concluded that H pylori infection increases the risk for development of gastric ulcers and they develop through the progression of gastric mucosal atrophy [30].

HYPERPLASTIC POLYPS

Hyperplastic polyps are a relatively rare complication of chronic gastritis. They may be multiple or single.

H.PYLORI ASSOCIATED HYPERTROPHIC GASTROPATHY

Hypertrophic gastropathies with features of Menetrier's disease may associate with H. pylori infection, suggesting that Hypertrophic gastropathy represents a special form of H.pylori gastritis. Biopsies demonstrate the presence of a chronic or chronic active gastritis with or without ulceration [4].

GASTRIC MALT LYMPHOMA

In recent years a significant increase in the incidence of primary Gastric lymphoma has occurred perhaps reflecting the association with H pylori infection. MALT Non-Hodgkins lymphomas emerge from areas of follicular gastritis associated with H pylori infection. Low-grade B-cell gastric MALT Lymphoma cellular proliferation can be stimulated by H pylori infection. This effect has been found to be strain specific and T cell-mediated response. Tumor-infiltrating T cells recognize H pylori and help stimulate tumor cell proliferation. This finding partly explains the clinical regression of primary low-grade B-cell gastric MALT Lymphoma after eradication of helicobacter pylori [4].

GASTRIC CANCER

The familial clustering of gastric carcinoma may result, in part from familial H. pylori infections. Such infections give rise to gastritis and intestinal metaplasia which then undergoes further genetic alterations leading to the development of gastric cancer. The previous study by Yoshimura T *et al.;* has shown that infection with H. pylori increased the number of apoptotic cells in the gastric mucosa. Apoptosis detected by Terminal Uridine deoxy nucleotide Nick End Labelling (TUNEL) technique shows DNA breaks in nuclei resulting from elimination of severely damaged DNA. Therefore, H. pylori infection might also be an initiator of gastric cancer by inducing epithelial DNA damage [31].

In a study conducted by Liu Y *et al.;* atrophy or metaplastic changes were seen largely limited to antrum and much less pronounced in corpus biopsies. The overall prevalence of atrophy and intestinal metaplasia in a country mirrored the respective incidence of gastric cancer, which is consistent with the hypothesis that chronic H.pylori associated inflammation is a key factor in gastric carcinogenesis.

In addition, it was also found that atrophy and intestinal metaplasia appeared at younger ages in higher risk populations. Authors also found that the prevalence of atrophy and intestinal metaplasia was strikingly low in Thailand (12% and 6% respectively), which corresponded to very low gastric cancer incidence in this country [32].

TREATMENT

Treatment is required only in patients who have a positive test result for *H pylori* infection and patients should be educated regarding the importance of completing the prescription and about the potential adverse effects of the medications. One of the most important factors to be considered when selecting the treatment regimen is drug resistance. Administer triple therapies for 10-14 days. The treatment regimens are omeprazole, amoxicillin, and clarithromycin (OAC) for 10 days; bismuth subsalicylate, metronidazole, and tetracycline (BMT) for 14 days; and lansoprazole, amoxicillin, and clarithromycin (LAC), which has been approved for either 10 days or 14 days of treatment.

CONCLUSION

Histopathological examination of gastric biopsies, apart from providing a clue to H.pylori infection, also indicates glandular atrophy and intestinal metaplasia, which are significant precursor lesions to the development of Gastric carcinoma in a long-standing duration. Thus these cases should be kept on a follow-up protocol. Antral biopsies are quite a reliable indicator of H pylori infection and H pylori associated lesions.

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