International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

H Pylori Associated Chronic Gastritis and Carcinogenic Effect

Dr. Gayathri Elanchezhian[1], DR. Thanka .J[2], Dr. S. Mary Lilly[3]

Postgraduate, Vice principal & Professor, HOD & Professor
Department of Pathology, Sree Balaji Medical College and Hospital, Bharath University

Corresponding Author: Dr. Gayathri .E

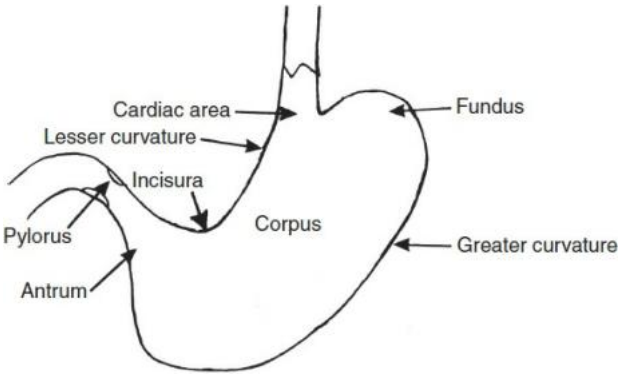
Abstract: ***Helicobacter pylori is one of the most common infection worldwide.* H. pylori *is a Gram-negative spiral-shaped organism with a flagella, it has been identified as an etiologic factor in the development of peptic ulcer disease because it may colonise in the human gastrointestinal system. Gastric neoplasms such as gastric adenocarcinomas and gastric mucosa-associated lymphoid tissue lymphomas have been linked to H pylori infection. Sensitive and precise diagnostic methods are required for effective antimicrobial treatment. This study summarizes current knowledge about the etiology of chronic gastritis, gastric intestinal metaplasia, and gastric cancer caused by Helicobacter pylori.***

Keyword: Helicobacter pylori, gastric adenocarcinomas, gastric mucosa-associated lymphoid tissue lymphomas

1.Introduction

Warren and Marshall[1] hypothesized a link between Helicobacter pylori with peptic ulcer disease and gastric cancer in 1983. In February 1994, the National Institutes of Health Consensus Development Conference concluded that H. pylori infection is the leading cause of peptic ulcer disease and that all patients with a proven peptic ulcer caused by H. pylori infection should be treated with antibiotics[2]. Unless the H pylori infection is cleared, the chance of an ulcer recurrence and complications increases. H. pylori was categorised as a group I human carcinogen by the International Agency for Research on Cancer Working Group of World Health Organization in June 1994, indicating its importance in global infectious diseases. The first bacterial pathogen to have its whole genome sequenced from two separate strains was Helicobacter pylori[3]. The prevalence rate varies, with developing countries having a greater incidence and developed countries having a lower rate. This virus spread from person to person by fecal oral route, oral-oral as well as environmental transmission through a contaminated water supply.

Normal Gastric Histology:



Gastric histology is divided into mucosa, submucosa, muscularis propria amd serosa. Mucosa has surface epithelium, lamina propria amd muscularis mucosa. The surface epithelium is lined by tall columnar and mucus secreting cells. The lamina propria composed of collagen and elastic fibres seen between the foveola. It contains capillaries, arterioles and nerve fibres. The submucosa is located between muscularis propria and muscularis mucosa consisting of loose connective tissue. Muscularis propria has three layers: outer longitudinal, inner circular and innermost oblique.

Histopathology of Helicobacter pylori-Induced Chronic Gastritis:

H. pylori are spiral-shaped or curved bacilli present in gastric biopsy specimens of almost all patients with with gastric ulcers or chronic gastritis. Acute H. pylori infection does not produce significant symptoms in most cases, only chronic gastritis causes the individual to seek treatment[4]. Antrum most common part affected in H pylori infection but long-standing cases may progress to involve the gastric body and fundus. This may result in atrophic gastritis with reduced parietal cell mass and intestinal metaplasia which has to be differentiated from autoimmune gastritis. Atrophy induced by H. pylori is not associated with autoantibodies and is typically patchy in contrast to autoimmune gastritis. The loss of parietal cells leads to reduced acid secretion that in turn stimulates gastrin production. Though there is loss of parietal cells, the increase in gastrin secretion is not that high as it is seen in autoimmune gastritis. Nevertheless, decreased acid secretion in H. pylori gastritis with atrophy reduces the risk of gastric and duodenal ulcers. This results in an inverse relationship between gastric adenocarcinoma, which is associated with atrophy and intestinal metaplasia and duodenal ulcers which are associated with increased acid secretion.

About 30% of individual gets affected by age of 50yrs and recently the prevalence of H pylori infection has been declining in developing countries due to improved sanitary conditions and use of antibiotics. The foveolar epithelium produces a thick layer of mucus that plays a protective role. H pylori normally colonize at this mucus layer so it attaches to surface mucous cells but does not penetrate deeper

layers. In chronic infection, H. pylori causes surface epithelial damage producing degenerative changes and cells appear cuboidal with loss of apical mucin content contacts. Occasional shows "Drop outs" due to loss of epithelium appearing as a small gap in the epithelium. In stomach, the most common affected site is antrum but in chronic state in can affect any part of the stomach causing gastritis. During active stage, marked neutrophilic infiltration seen in mucous neck region and lamina propria in early stage and as the severity increases it aggregates in pit lumen to form pit abscess. After treatment, the bacteria migrate from antrum to corpus, decreasing the activity of antral gastritis. In order to replace the dying cell, the mucous neck cells proliferate and characterized by loss of mucin, increased mitosis, basophilic cytoplasm and hyperchromatic nuclei mimicking dysplasia. The characteristic histological feature of H pylori infection is neutrophilic inflammation and presence of lymphoid follicles.[5]

H pylori can be detected by rapid urease test, Histology, Bacterial culture and sensitivity test, Stool antigen test, Polymerase chain reaction to detect bacterial loads and identify mutations associated with antimicrobial resistance. Special stains such as Giemsa and Warthin starry stain with immunohistochemistry for H pylori are commonly used.

Grading the Helicobacter pylori-Induced Chronic Gastritis:

The most widely used grading system for H pylori is updated Sydney scoring system which includes H pylori density, intestinal metaplasia, activity, chronic inflammation and glandular atrophy. Each feature is assigned either a numeric value: 0 for absent, 1 for mild, 2 for moderate 3 for marked (or severe).

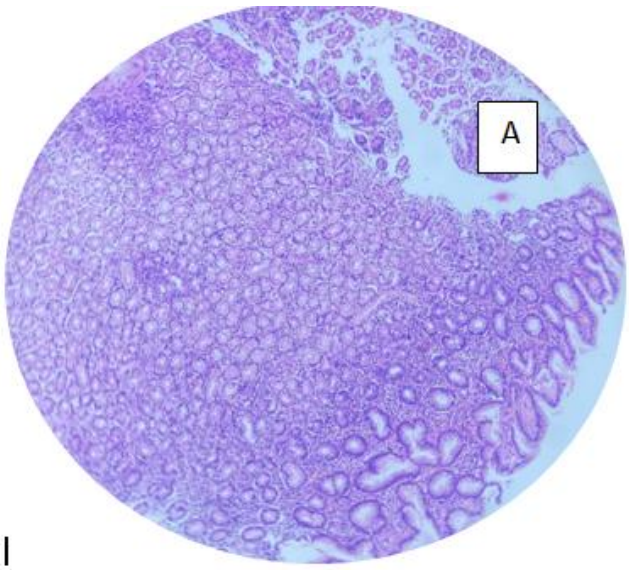


Figure A: gastric mucosa with lymphoid collection in the lamina propria

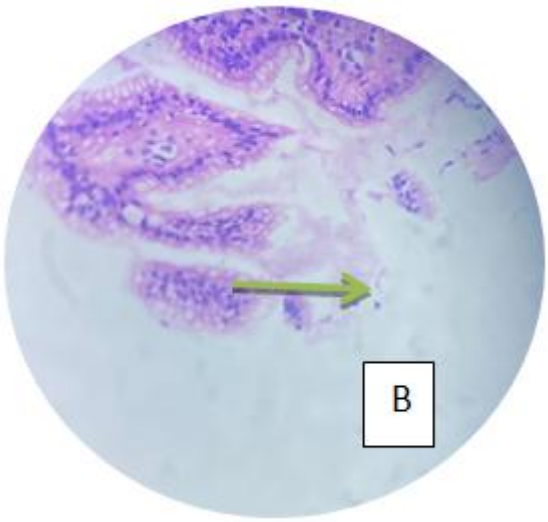


Figure B: H pylori organism in H&E stain

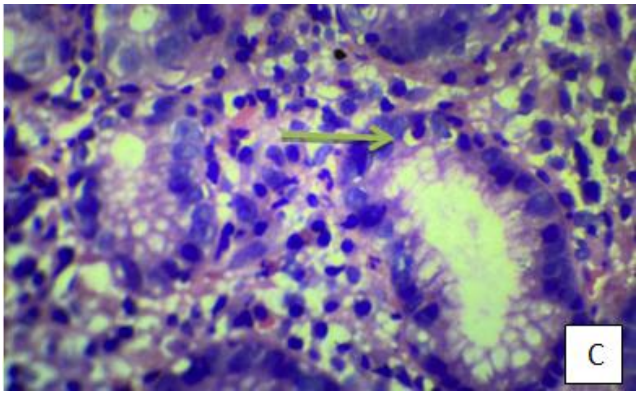
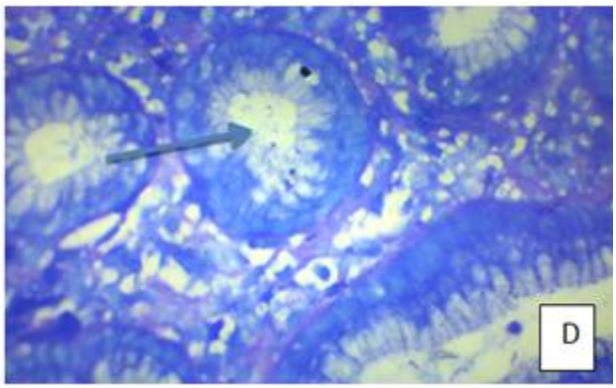


Figure C: presence of neutrophils within glands representing activity



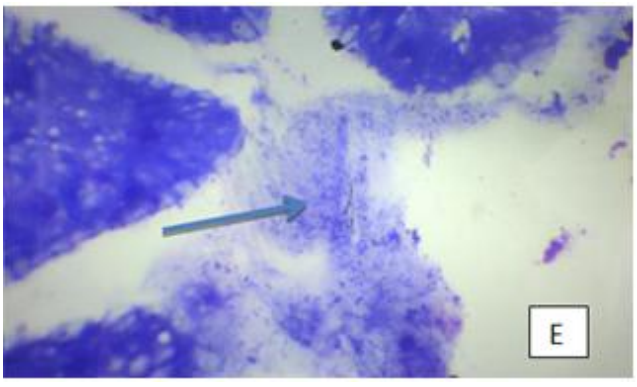
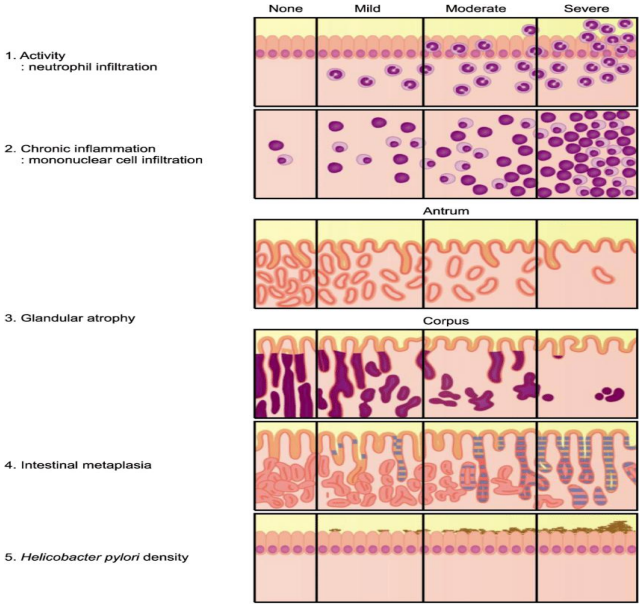


Figure D & E: Giemsa stain showing H pylori organism



Helicobacter pylori-Induced Chronic Gastritis and Sydney System Multistep Cascade of Gastric Carcinogenesis:

The antrum is the preferred biopsy site for evaluation of H. pylori gastritis because it is most commonly infected. In dense colonization, organisms may also be found in oxyntic (acid-producing) mucosa of the fundus and body. H. pylori–infected antral mucosa is usually erythematous and has a coarse or even nodular appearance. The inflammatory infiltrate includes large numbers of plasma cells, often in clusters or sheets, within the superficial lamina propria. These are accompanied by increased numbers of lymphocytes, macrophages, and neutrophils within the lamina propria. Neutrophils infiltrate across the basement membrane and accumulate in the lumens of gastric glands, or pits, to create pit abscesses. When intense, inflammatory infiltrates may create thickened rugal folds, mimicking the endoscopic appearance of early cancers. Lymphoid aggregates, some with germinal centers, are frequently present and represent induced mucosa-associated lymphoid tissue (MALT) that has the potential to transform into lymphoma. Thus, chronic H. pylori gastritis is associated with increased risk of both gastric adenocarcinoma and lymphoma.

The mechanism for H pylori causing gastric carcinoma is similar to hepatitis B & C virus inducing hepatocellular carcinoma, where there is increased epithelial proliferation in the background of chronic inflammation. The inflammatory environment contains many genotoxic agents inducing carcinogenesis in H pylori genome and various genes are also directly involved in the carcinogenesis. The gene involved in H pylori associated gastric carcinoma is Cag A (cytotoxin-associated antigen A).6 which initiates the signalling pathway resulting in uncontrolled growth factor activation. The spectrum disease is chronic gastritis followed by gastric atrophy, intestinal metaplasia, dysplasia and malignancy.

H pylori also causes gastric lymphoma with B cell origin which is mainly due to host genetic factors and specific characteristic of H pylori strain such as polymorphisms in the promoters of inflammatory cytokines like IL-1 and TNF. This infection will cause activation of polyclonal B cell growth and then mature into MALToma, which is dependent on T-cell activation of B-cell pathways through transcription factor nuclear factor kappa light chain enhancer of activated B (NF-κB). Antibiotic therapy at this point will cure lymphoma by removing the trigger. After NF-κB activation due to further mutation at this point it doesn't require further antigenic stimulus of the bacterium for growth and survival and develops the capacity to spread beyond the stomach to other tissues.

2.Conclusion

This review highlights the pathogenesis of H pylori associated gastritis and its carcinogenic effect in adenocarcinoma and MALToma. Histopathological interpretation of gastric biopsies is a reliable indicator of H pylori infection as well as gastritis grading according to the Sydney grading system. Early eradication of H pylori will improve the overall survival rate.

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