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The Retroactive Heartburn-Gastro-Oesophageal Reflux Disease

Anubha Bajaj*

Department of Histopathology, Panjab University, India

***Corresponding Author:** Anubha Bajaj, Department of Histopathology, Panjab University, India.

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Preface

Gastro-oesophageal reflux disease (GERD) is a disorder emerging from a retrograde influx of gastric contents, depicts specific symptoms and complications and is commonly relieved with the administration of antacids. Gastro-oesophageal reflux disease (GERD) is a frequently engendered oesophagitis arising on account of reflux of gastric or duodenal contents within the lower oesophagus.

Delayed complications include mild to moderate mucosal haemorrhage, configuration of oesophageal strictures, Barrett's oesophagus and a probability of Barrett's ulcer. Barrett's oesophagus emerging on account of gastro-oesophageal reflux disease (GERD) is a complication with malignant overtones. Barrett's oesophagus typically arises in middle-aged, white males and necessitates surveillance in order to exclude metamorphosis into dysplasia or overt malignancy.

Disease characteristics

Gastro-oesophageal reflux disease (GERD) can be designated into erosive and non-erosive categories. It can exemplify as a non-erosive reflux disease (NERD) where the characteristic symptoms of gastro-oesophageal reflux (GERD) appear in the absence of distinctive mucosal injury. Aforesaid mucosal damage can arise during an endoscopic procedure or emerge as an erosive oesophagitis with specific histological manifestations within the oesophageal mucosa. Mucosal erosion of the oesophagus can be engendered as a constituent of reflux esophagitis [1,2].

Gastro-oesophageal reflux disease (GERD) is a frequent condition and demonstrates a prevalence varying from 3% to 40% in North America with enhanced incidence in Northern Iran and China. Commonly adults exceeding > 40 years of age are implicated and the disease is mild to moderate. Incidence of gastro-oesophageal reflux (GERD) amplifies with age and is markedly elevated beyond 40 years. Younger individuals may be occasionally incriminated. Emerging as a mild disorder in a majority of implicated adults, gastro-oesophageal reflux disease can display oesophageal mucosal injury or reflux oesophagitis in approximately one third (34%) of individuals [1,2].

Although devoid of a gender predisposition, gastro-oesophageal reflux is predominantly associated with complications in the male subjects. Oesophagitis emerges with an estimated proportion of 2: 1 and metamorphosis into Barrett's mucosa is around 0.1, as encountered in males.

Concurrent obesity enhances the risk of gastro-oesophageal reflux (GERD), erosive oesophagitis and oesophageal carcinoma. Proportion of erosive disease is enhanced with increasing body mass index (BMI) [1,2].

Disease pathogenesis

Acid reflux is transient, normal and asymptomatic, especially within the post prandial phase. However, gastro-oesophageal reflux (GERD) can be initiated with elevated threshold of acid reflux. Chronic exposure and susceptibility to gastric secretions impairs the

regenerative potential of oesophageal mucosa and mucosal injury on account of gastric acid, a fact which is critical to the genesis of gastro-oesophageal reflux. Reflux of bile and bile acids can be contributory to reflux disease [3,4].

Gastro-oesophageal reflux is generated on account of decimated efficiency of oesophageal anti reflux mechanisms, particularly the muscle tone of lower oesophageal sphincter, which is the predominant barrier to acid reflux. Consumption of alcohol and central nervous system depressants such as clomipramine enhances possible occurrence of reflux disease. Associated risk factors enumerated are delayed gastric emptying, hypothyroidism, insertion of a nasogastric tube, pregnancy, sliding hiatal hernia, systemic sclerosis and tobacco intake [3,4].

Factors implicated in the emergence of gastro-oesophageal reflux disease are

- Deranged function of lower oesophageal sphincter (LES): The lower oesophageal sphincter (LES) provides an anti reflux barrier within the gastroesophageal junction, thereby circumventing retrogressive entry of gastric acid into the oesophagus. A proportion of physiological gastro-oesophageal reflux occurs in healthy individuals due to transient relaxation of LES, especially following consumption of food, in order to allow gaseous egress from the gastric cavity. Gastro-oesophageal reflux (GERD) is associated with an augmentation of transient relaxation of LES in accompaniment with a declining pressure within the sphincter. Nevertheless, mechanics of enhanced transient relaxation of the sphincter remain obscure. Several pertinent probable causes for a decline in LES pressure are cogitated such as pregnancy, diabetes, scleroderma, obesity and administration of medications as with calcium channel blockers, cholinergic antagonists, glucagon, nicotine consumption and oral contraceptives [1,2].
- Hiatal hernia is a common, asymptomatic condition. Hiatal hernia in association with GERD demonstrates an elevated quantification of acid reflux along with a delayed efflux from the oesophagus. Enlarged hiatal hernia contributes to a reduced muscular tone of the LES. Hiatal hernia appears in an estimated one fourth (25%) of subjects with non-erosive gastro-oesophageal reflux (GERD), in around three fourths (75%) instances with erosive gastro-oesophageal reflux (GERD) and in a majority (> 90%) of individuals with Barrett's disease [1,2].
- Administration of refluxate with consequent irritant outcomes: pH of gastric acid reflux is beneath < 4 and extended contact of gastric contents with oesophageal mucosa initiates the oesophagitis. Also, reflux of bile or alkaline pancreatic secretions can incur mucosal degeneration.
- Aberrant oesophageal clearance: Gastric acid within the oesophagus is generally removed and neutralized on account of oesophageal peristalsis and bicarbonate ions secreted in the saliva. Oesophageal peristalsis is infrequent during sleep thereby prolonging the duration of accumulation of gastric acid within the oesophageal cavity with consequent mucosal injury. Consumption of alcohol and sedatives can decimate oesophageal peristalsis. Additionally, conditions such as Sjogren's syndrome which influence the quality or quantity of saliva besides anticholinergic agents or oral radiation which can bring about a deterioration of oesophageal protective mechanisms are also incriminated. Aforesaid disorders enhance the period of contact of gastric acid to the oesophageal mucosa, thereby augmenting mucosal damage [1,2].

Clinical elucidation

Characteristic clinical symptoms are comprised of heartburn and dysphagia whereas emerging pain can be misconstrued for myocardial infarction. A daily enunciation of clinical symptoms is delineated in around 7% subjects, weekly representation appears in nearly 14% individuals and a monthly exemplification of classical symptoms is exhibited in roughly 15% to 40% of instances [4,5].

Categorical clinical manifestations of gastro-oesophageal reflux (GERD) are denominated as heartburn, regurgitation of gastric and oesophageal contents and dysphagia. Additionally, symptoms such as globus sensation (lump in the throat), odynophagia and nausea can ensue. Typical symptom of gastro-oesophageal reflux as designated with heartburn is commonly enunciated around 30 minutes to 60 minutes following a meal, especially upon a recumbent position. Heartburn is designated as a characteristic, postprandial, retrosternal burning or a discomfort chiefly localized within the epigastric region and a superior radiation towards the neck. Postural modifica-

tions such as forward bending or ingestion of specific foods or beverages as with ketchup, chocolate, coffee, tea or alcohol can aggravate the symptoms [5,6].

Atypical clinical representation ensures the emergence of pertinent extra-oesophageal symptoms as cogitated with pulmonary, ear, nose or throat manifestations along with the emergence of non-cardiac chest pain [5,6].

Histological elucidation

Histological manifestations are not concurrent with severity of clinical symptoms. On gross examination, severe instances display a hyperaemic oesophageal mucosa with foci of haemorrhage. Squamous epithelium of the oesophagus can be damaged due to acidic reflux. Minimal diagnostic criterion for determining gastro-oesophageal reflux lack consensus.

Mild disease can singularly demonstrate mucosal hyperaemia. An estimated one third (34%) subjects with symptoms of chronic gastro-oesophageal reflux (GERD) can delineate normal endoscopic features. Inflammatory cells such as eosinophils, neutrophils and predominant T lymphocytes appear within the squamous epithelial layer. Basal cell hyperplasia is cogitated which approximately exceeds 15% to 20% of thickness of squamous epithelium [6,7].

Additionally, elongation of papillae of lamina propria within the upper one third of squamous epithelium and ballooning of squamous cells in around three fifth (65%) instances can be discerned. Ballooning of squamous cells can recapitulate glycogenic acanthosis, however, squamous cells of gastro-oesophageal reflux are non reactive to Periodic acid Schiff's (PAS) stain and reactive to immunoglobulins or albumin [6,7].

Vascular dilatation is enunciated within three fifths (60%) of instances, particularly within the superficial papillae. Vascular dilatation can also be associated with oesophageal varices. Multinucleated giant cells arising from the squamous epithelium can simulate a viral cytopathic effect [6,7].

Gastro-oesophageal junction is devoid of interstitial cells of Cajal. Eosinophils within the lamina propria are preliminarily enunciated in around 30% instances. However, infiltration of eosinophils is infrequent in infants, appear in nearly half (52%) of the adults and is concordant with endoscopic features. Occasionally, eosinophils are exemplified within the normal lamina propria and in individuals with oesophagitis un-associated with gastro-oesophageal reflux. Eosinophils are challenging to detect with the employment of Bouin or Hollande fixative, employed for histological processing. Exceptionally, presence of innumerable eosinophils can recapitulate eosinophilic esophagitis. Infrequent emergence of eosinophils are delineated in roughly one third (34%) of normal adults. Thus, although an unreliable diagnostic feature, rare emergence of eosinophils within uninvolved subjects can be indicative of subclinical disease and impending gastro-oesophageal reflux (GERD) and can be contemplated as a morphological assessment which can be categorized within an appropriate clinical context [1,2].

Neutrophils appear in around 15% instances and are indicative of a severe mucosal injury especially mucosal ulceration and erosion. Fungal infection requires an exclusion in the presence of significant quantities of neutrophils or a purulent exudate.

Lymphocytes are considered to be a normal constituent of squamous epithelial mucosa and enunciation of T lymphocytes is an insignificant microscopic feature.

Cardiac mucosa can appear at the gastro-oesophageal junction. Gastro-oesophageal reflux disease (GERD) can exemplify mucosal alterations indicative of infection with Helicobacter pylori such as infiltration with neutrophils, plasma cell or eosinophils [2,3].

Differential diagnosis

Gastro-oesophageal reflux disease (GERD) requires a segregation from various conditions such as eosinophilic esophagitis, infectious esophagitis, epithelial hyperplasia of the normal oesophagus, oesophagitis induced due to intake of pills and radiation or chemotherapy induced esophagitis [2,4].

Investigative assay

Pre-emptively, diagnostic evaluation is unnecessary for discerning symptoms typical of gastro-oesophageal reflux (GERD). However, appearance of "alarm symptoms" such as significant dysphagia, odynophagia, weight loss, iron deficiency anaemia and persistence of clinical symptoms despite empiric proton pump inhibitor therapy mandate suitable investigations. Subjects with diabetes mellitus can enunciate dyspepsia, especially during a myocardial infarction. Thus, emergence of acute clinical symptoms mimicking a gastro-oesophageal reflux require appropriate evaluation [6,7].

Radiographic assessment is of limited utility in the discernment of gastro-oesophageal reflux disease (GERD). Mild reflux depicts a poor radiographic sensitivity although a moderate to severe oesophagitis, oesophageal stricture, hiatal hernia and tumours can be adequately detected.

Barium swallow is a frequently utilized procedure which can adequately assess the oesophagus or upper gastrointestinal tract with evaluation of the oesophagus, stomach and small intestines [7,8].

Upper gastrointestinal endoscopy can exclude adjunctive diseases such as gastrointestinal tumours and peptic ulcer besides the detection and gradation of severity of gastro-oesophageal reflux (GERD) induced esophagitis. Upper gastrointestinal endoscopy demonstrates an estimated 90% to 95% specificity for discernment of GERD whereas the sensitivity is around 50% [1,2].

Assessment of oesophageal pH or combined oesophageal impedance testing is generally not required although the investigation may be indicated in subjects delineating atypical or extra-oesophageal symptoms or individuals contemplating anti-reflux surgery. Intra-oesophageal pH monitoring can be employed to discern the presence of gastric acid. Bernstein acid infusion test can be adopted to evaluate sensitivity of oesophageal mucosa to the presence of gastric acid. Impedance testing can suitably distinguish the alterations in electrical current resistance upon the placement of an oesophageal catheter. In addition to assaying the oesophageal pH, aforesaid catheter can differentiate betwixt antegrade and retrograde transport of gases and liquids. Impedance testing is beneficial in individuals of debatable gastro-oesophageal reflux (GERD) with non-reactive assays of oesophageal pH and inconclusive results of standardized investigations. Failure to demonstrate significant gastro-oesophageal reflux (GERD) accompanied by typical or atypical symptoms and instances of refractory gastro-oesophageal reflux (GERD) can benefit with assessment by impedance testing [1,2].

Endoscopic evaluation demonstrates the presence of linear ulcers appearing within the distal oesophagus usually in association with mucosal exudate, erythema or oedema. Aforesaid endoscopic features are normal in around half (50% to 60%) of symptomatic subjects. A histological assessment is required in clinically indicative instances of reflux esophagitis, although aforesaid instances may be accompanied by normal endoscopic features [1,2].

Multiple tissue specimens are required for cogent histological evaluation as mucosal modifications can be non-specific. However, a concordance betwixt various diagnostic modalities is lacking and currently the disorder is devoid of a diagnostic "gold standard".

Therapeutic options

Therapeutic intervention of gastro-intestinal reflux (GERD) is aimed at resolution of typical symptoms, alleviation of oesophagitis and circumventing disease complications. Specific treatment for gastro-oesophageal reflux disease (GERD) is comprised of administration of agents which enhance oesophageal motility, administration of Histamine-2 (H2) receptor antagonists, proton pump inhibitors and surgical intervention to reduce the proportion and degree of hiatal hernia. Cogent therapies also comprise of lifestyle modifications, medical treatment with antacids or anti secretory agents and adoption of mechanical therapies [7,8].

Alterations in lifestyle incorporate maintenance of appropriate body weight, head elevation, cessation of tobacco, alcohol and symptoms aggravating foods with prevention of delayed meals.

Medical therapies are constituted of administration of anti-secretory agents and antacids which are efficacious, accessible and cost effective. Histamine-2(H2) receptors antagonists prohibit gastric acid secretion by competitive blockage of H2 receptors which are situated within the gastric parietal cells. H2 blockers are efficacious in approximately three fourths (75%) subjects with mild to moderate oesophagitis [7,8]. Proton pump inhibitors (PPI) function as a blocking agent of hydrogen- potassium ATPase located upon the apical surface of parietal cells. Proton pump inhibitors are superior to H2 blockers as they predominantly influence the common pathway of acid secretion. Proton pump inhibitors can be employed as initial therapy in moderate to severe gastro-oesophageal reflux (GERD) and reflux with complications. Complications of gastro-oesophageal reflux are comprised of mucosal haemorrhage and oesophageal strictures. Adoption of histamine-2 receptor antagonists and proton pump inhibitors demonstrate enhanced proportion of mucosal healing and a decline in disease relapse.

Surgical maneuvers applicable for anti-reflux mechanisms are constituted of laparoscopic fundoplication and variant methodologies of bariatric surgery for managing obesity. Fundoplication provides an excellent symptomatic relief and alleviation of oesophagitis in a majority (> 85%) of subjects. Fundoplication surgery demonstrates inferior outcomes in individuals with extra-oesophageal symptoms of gastro-oesophageal reflux [7,8].

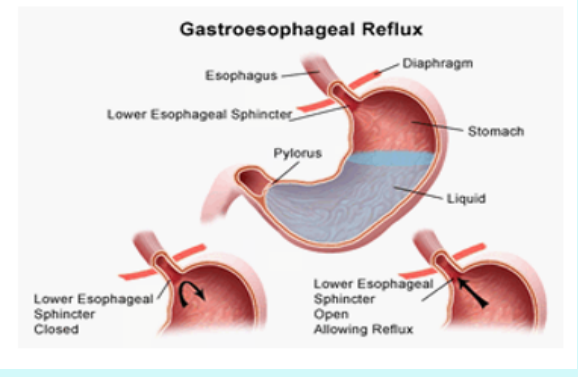

Figure 1: *GERD with comparisons of normal oesophagus and deficient lower oesophageal sphincter permitting acid reflux [9].*

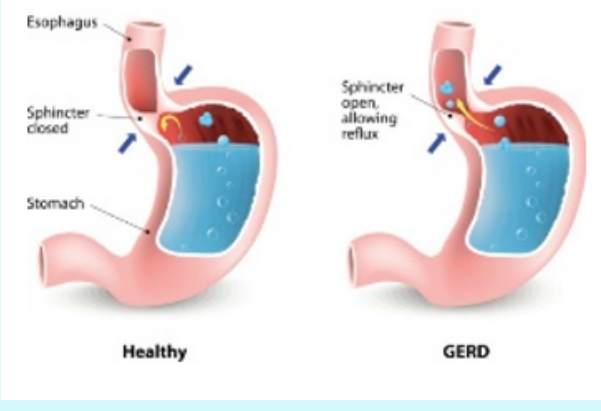

Figure 2: *GERD with demonstration of a normal and diseased lower oesophageal sphincter allowing relax of gastric chyme [10].*

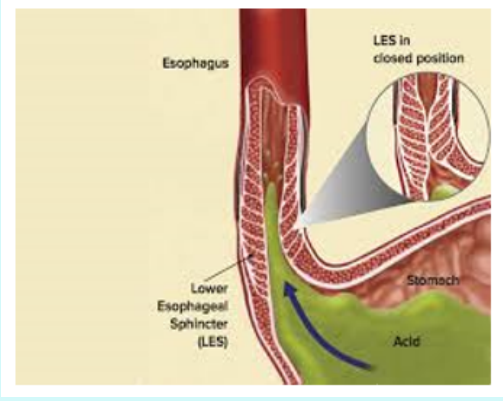

Figure 3: *GERD displaying the positioning of lower oesophageal sphincter with consequent reflux of gastric secretions [11].*

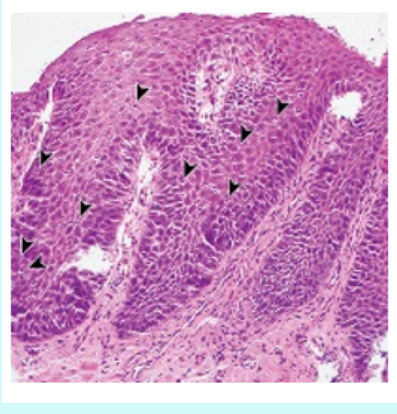

Figure 4: *GERD demonstrating basal cell hyperplasia, mucosal injury and lymphocytic infiltration within the oesophagus [12].*

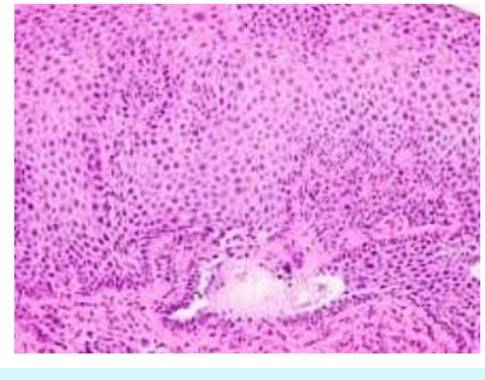

Figure 5: *GERD delineating mucosal erosion, basal cell hyperplasia and inflammatory infiltrate within the squamous epithelium [13].*

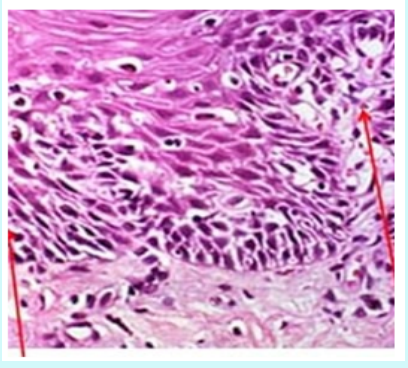

Figure 6: *GERD with significant basal cell hyperplasia and moderate lymphocytic infiltrate within the squamous epithelium [14].*

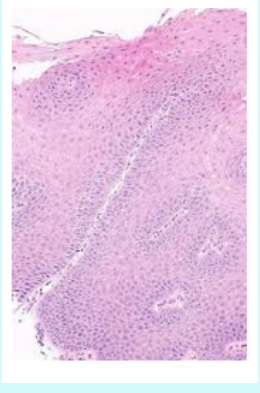

Figure 7: *GERD with mild inflammatory exudate of neutrophils, eosinophils and lymphocytes, mucosal deterioration and basal cell hyperplasia [15].*

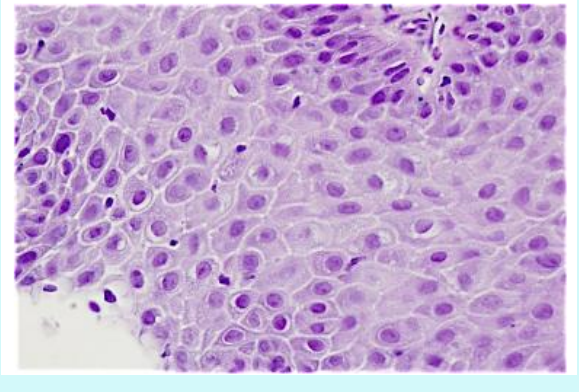

Figure 8: *GERD with basal cell hyperplasia and patchy, chronic inflammatory exudation of lymphocytes within the acanthotic squamous epithelium [16].*

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9. Image 1 Courtesy: CHOC Children.
10. Image 2 Courtesy: Academy of nutrition and diabetes.
11. Image 3 Courtesy: UT health Austin.
12. Image 4 Courtesy: AMA Ed Hub.
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15. Image 7 Courtesy: Libre Pathology.
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