Research Paper
Impact Factor: 3.567
Peer Reviewed Journal

IJMDRR
E- ISSN –2395-1885
ISSN -2395-1877

ANALYSIS OF UPPER GASTROINTESTINAL TRACT BIOPSIES FROM PATIENTS WITH GERD SYMPTOMS

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Abstract

A spectrum of pathological changes is observed in upper gastrointestinal biopsies of patients presenting with gastroesophageal reflux disease (GERD). Some of these entities carry an increased risk of progression to malignancy and hence, it is vital to identify the risk factors of these conditions, provide screening facilities and follow-up the high risk group of patients.

Objective of the present study was to analyze the endoscopic biopsies of patients who presented with GERD symptoms. A retrospective study done over a period of 3 years at a tertiary care hospital. The study sample consisted of 141patients who were subjected to upper gastrointestinal endoscopic examination and subsequent biopsy sampling. Results showed that majority of the cases comprised of reflux oesophagitis (62.40%), and included both erosive and non erosive forms of the disease. Barrett oesophagus which is being increasingly recognized was diagnosed in 21 (14.89%) cases who had unequivocal evidence of goblet cell metaplasia. There were nine (6.38%) cases of low grade dysplasia and three (2.12%) cases of high grade dysplasia. Prevalence of oesophageal adenocarcinoma was 0.7 %. Gastroesophageal reflux disease is becoming more prevalent worldwide. Identification of the serious long term complications of this condition requires regular follow-up of high risk patients.

Key Words: Gastroesophageal Reflux Disease, Reflux Oesophagitis, Barrett Oesophagus, Intestinal Metaplasia.

Introduction

Upper gastrointestinal biopsies are increasingly being performed for patients presenting with symptoms of gastroesophageal reflux disease (GERD), in view of identifying the magnitude of the disease and any associated complications [1].Transient reflux is normal, especially postprandial, but usually asymptomatic. Excessive retrograde movement of acid-containing gastric secretions or bile and acid mixed secretions from the duodenum and stomach into the esophagus is an important etiologic factor of GERD. Gastroesophageal reflux results in chronic mucosal inflammation and damage and impairs the reparative capacity of the oesophageal mucosa [2].

The lower oesophageal sphincter (LES) plays an important role in the prevention of reflux of gastric secretions [3]. The lower oesophageal sphincter is normally located in the abdomen. The diaphragmatic crura functions as an external sphincter and supports the actions of the LES. LES dysfunction occurs due to transient or permanent relaxation of the sphincter or increased intra abdominal pressure. Delayed gastric emptying is another important factor that contributes to reflux of gastric contents. Delayed gastric emptying increases the intra gastric pressure, thus exerting more tension on the LES. Another condition which is frequently encountered in patients with GERD is hiatal hernia [4].A hiatal hernia occurs when a portion of the stomach prolapses through the diaphragmatic oesophageal hiatus.Most hiatal hernias are asymptomatic and are discovered incidentally. These hiatus hernias are classified either as sliding hernias or paraesophageal hernias. Approximately 99% of hiatal hernias are sliding, and the remaining 1% are paraesophageal. Hiatal hernia usually pushes the LES proximally into the thoracic cavity. In this position the LES loses the external sphincteric action of diaphragmatic crura. The incidence of hiatal hernia increases with age. Proper oesophageal clearance is another important factor that helps to prevent mucosal injury. Normal oesophageal clearance minimizes the time that the oesophageal mucosa is exposed to refluxed gastric secretions. Peristalsis helps in achieving mechanical clearance and saliva is useful for chemical clearance of the oesophagus. It has been found that peristaltic dysfunction is associated with the development of oesophagitis [5].

Several studies have shown that GERD is more prevalent in people who are morbidly obese [6]. A high body mass index is a risk factor for the development of GERD [7]. Morbid obesity leads to increased intragastric pressure and gastroesophageal pressure gradient [8, 9]. In addition, obesity is increasingly associated with transient relaxation and malfunctioning of the LES. Zollinger-Ellison syndrome which is associated with increased gastric acidity due to gastrin hormone production is another important risk factor for the development of chronic mucosal damage and oesophagitis.

Certain types of food and the lifestyle are considered to promote gastroesophageal reflux disease. Foods that have been implicated in GERD include coffee, alcohol, chocolate, fatty foods, acidic foods, and spicy foods. Moderate exercise

improves symptoms, however in those with GERD vigorous exercise may worsen the symptoms. Smoking aggravates GERD by causing transient relaxation of the lower oesophageal sphincter.

Pathological conditions associated with GERD include a wide spectrum of disease entities with adenocarcinoma at the lower endofoesophagus being the worst possible outcome [10]. Adenocarcinoma of the lower end of oesophagus is increasingly being recognized, and considered to be almost always associated with Barrett's oesophagus. The type of oesophageal carcinoma has been changing for some time with adenocarcinoma becoming more prevalent. Biopsy interpretation of lower oesophageal biopsies is likely to reveal any of the following entities [11].

- Oedema and basal cell hyperplasia – nonspecific inflammatory changes
- Lymphocytic inflammation -nonspecific finding
- Neutrophilic inflammation - usually due to reflux or *Helicobacter pylori* associated chronic gastritis
- Eosinophilic inflammation (usually due to reflux) - The presence of intraepithelial eosinophils in high density may suggest a diagnosis of eosinophilic oesophagitis(EE).An eosinophil count of less than 20 eosinophils per high-power microscopic field in the distal esophagus and in the presence of other histological features of GERD, is more consistent with GERD than EE.
- Goblet cell intestinal metaplasia /Barrett's esophagus
- Elongation of the papillae
- Erosive oesophagitis
- Thinning of the squamous cell layer
- Dysplasia (low or high-grade)
- Carcinoma

Objectives

The aim of this study was to analyze the histological features of the upper gastrointestinal tract biopsies, in view of identifying the spectrum of pathological entities in patients presenting with GERD symptoms.

Methodology

A retrospective study done over a period of 3 years (from January 2012 to January 2015) at the Department of pathology, Faculty of Medical Sciences, University of Sri Jayewardenepura. Data was collected from the histopathology reports of the endoscopic biopsies of patients who presented with symptoms of GERD during the specified study period. Upper gastrointestinal biopsy specimens which were received during the study period have been processed following adequate fixation. Biopsy sites have been labeled and put in to separate tissue cassettes. Following routine tissue processing serial tissue sections were prepared and stained with hematoxylin & eosin. Alcian blue special stain has been used for the identification of goblet cell metaplasia.

The histological diagnoses were reviewed by the principal investigator and the results were tabulated using a coding system. Data was gathered from the laboratory reports without revealing the identification details.

Results

The retrospective study sample consisted of 141 patients who were subjected to upper gastrointestinal endoscopic biopsies. Histological findings were categorized in to seven groups (table 01).

Table 01: Histological Analysis of the Upper Gastrointestinal Biopsies of Patients with GERD Symptoms

Histological diagnosis	Number of patients	Percentage
Non-specific inflammation	19	13.47%
Reflux oesophagitis (non-erosive)	68	48.22%
Reflux oesophagitis (erosive)	20	14.18%
Goblet cell metaplasia (Barrett oesophagus)	21	14.89%
Low-grade dysplasia	09	6.38%
High-grade dysplasia	03	2.12%

Discussion

There are no minimum criteria to diagnose gastroesophageal reflux disease.Histological abnormalities of reflux oesophagitis may or may not be detected by endoscopy. Up to 1/3 of patients with chronic GERD symptoms have normal endoscopic biopsies. In very mild disease hyperemia may be the only histological finding.

In this study, non-specific findings such as mucosal oedema and the presence of a mild inflammatory infiltrate in the lamina propria was seen in 19 (13.47%) cases with symptoms of GERD.

Histological changes known to occur in reflux oesophagitis include intraepithelial inflammatory cells (neutrophils, eosinophils, excess lymphocytes), basal cell hyperplasia exceeding 15 – 20% of epithelial thickness, elongation of papillae into the upper 1/3 of the epithelium, vascular dilatation and ballooned squamous cells. There are no diagnostic criteria as to how many of these should be present to make a definitive diagnosis of reflux oesophagitis. Sixty-eight (48.22%) cases that were diagnosed with reflux oesophagitis (non- erosive) had at least two of the above mentioned changes, but not all of them. Erosive oesophagitis patients showed superficial mucosal damage and a neutrophilic exudate mixed with fibrinous material in addition to the usual histological features of reflux. In the present study erosive oesophagitis was seen in 20 (14.18%) cases who had symptoms of GERD.

Another well- recognized clinicopathological entity associated with long standing chronic irritation and inflammation of the lower oesophagus due to gastroesophageal reflux, is the development of metaplastic glandular changes. The disease is known as Barrett oesophagus, which may be asymptomatic in a large proportion of the population. Controversy exists with regard to the definition of Barrettoesophagus, as some researchers believe it should include only intestinal type metaplastic epithelium with goblet cells.The current definition for Barrett's esophagus proposed by the American Gastroenterological Association (AGA) is "the condition in which any extent of metaplastic columnar epithelium that predisposes to cancer development replaces the stratified squamous epithelium that normally lines the distal oesophagus [12]". Three types of columnar epithelium are seen in the setting of Barrett oesophagus: (I) gastric-fundic type (II) cardia-type and (III) intestinal-type including goblet cells. However, only the intestinal type of metaplasia is thought to be associated with an increased risk of progression to carcinoma. For this reason, both the American Gastroenterological Association and the American College of Gastroenterology recommend that although columnar-type mucosa can be recognized during endoscopy, the presence of intestinal metaplasia must be confirmed histologically to arrive at a diagnosis of Barrett oesophagus [12,13]. In this study there were 21 (14.89%) cases with histologically confirmed goblet cell metaplasia. Alcian blue special stain was used on biopsy specimens to highlight goblet cells.

Barrettoesophagusis identified endoscopically as salmon-pink coloured extensions, that grow into the esophageal mucosa above the gastroesophageal junction. In suspected Barrett oesophagus patients, ideally four quadrant biopsies should be taken form the squamo-columnar junction along with every 2 cm of Barrett type mucosa. Specimens must be sent in separate containers for histological assessment. Barrett oesophagusis termed long segment if the mucosal protrusions are 3 cm or more in length, short segment Barrett when less than 3 cm, and ultra-short segment Barrett when less than 1 cm[14]. The exact location of the biopsy in relation to the gastroesophageal junction is important to know, as ultra-short Barrett can be difficult to differentiate from an irregular squamo-columnar junction. And is thought to carry significantly less risk of cancer development than traditional BE[15, 16]. Additionally, intestinal metaplasia below the squamo-columnar junction should not be diagnosed as Barrettoesophagus. In this context the changes are thought to be associated with a different etiology, often arising secondary to *Helicobacter pylori* infection. In this setting the significance as a risk factor for the development of oesophageal adenocarcinoma is uncertain [17, 18].Hence the changes in this region should be given as a descriptive diagnosis.

Recent studies have shown that columnar cell metaplasia may have an intestinal-type immunohistochemical profile in the absence of goblet cells. Several studies have shown a significantly increased positivity for intestinal markers such as DAS-1[19], CDX-2 [20], and HepPar1in both goblet cell and non-goblet cell columnar epithelia, suggesting a similar origin. To support the above findings there have also been studies showing similar molecular alterations in both non-goblet cell and intestinal-type metaplasia including chromosomal instability [21], microsatellite instability [22], and similar DNA content abnormalities [23].However, the natural history of columnar cells and goblet cells is not always the same [24] suggesting that there are additional factors that contribute towards the development of dysplasia and malignancy.

It is of importance to recognize dysplastic changes when evaluating biopsies of patients with GERD symptoms. Biopsies were categorized in to following groups based on the cytoarchitectural features mentioned below.

Negative for dysplasia – Biopsies show a normal architecture. There is abundant lamina propria between the glands. Nuclei are regular and basally located. If mitoses are detected those will be confined to the basal layer. Mild inflammatory atypia may be present.

Indefinite for dysplasia – In this category the changes are in between reactive and low-grade dysplasia. These biopsies show background inflammation with or without focal superficial ulceration. Mucosal architecture is intact but there is nuclear overlapping, enlargement and hyperchromasia. However, the surface maturation is present.

Low grade dysplasia – There is absent or minimal surface maturation although the architecture is largely intact. An important feature of low grade dysplasia is cytologicatypia extending to the mucosal surface. In addition, there is mild glandular crowding. Mitoses may be increased but no atypical forms are seen. Preserved nuclear polarity is a useful finding to separate low grade dysplasia from high grade dysplasia.

High grade dysplasia – There is severe cytologicatypia characterized by nuclear enlargement and pleomorphism. Surface maturation and nuclear polarity are lost. There is mild to moderate architectural distortion. Mitoses are increased and atypical forms may be seen. Usually inflammation is minimal or absent.

In this study there were 09 (6.38%) cases with low grade dysplasia and 03 (2.12%) cases with high grade dysplasia. Whenever high grade dysplasia is detected the biopsy should be carefully evaluated and examined at multiple levels to exclude co-existing oesophageal adenocarcinoma. This may be difficult on biopsy specimens but any suspicious findings should be documented and promptly conveyed to the clinician. The prevalence of oesophageal adenocarcinoma in the present study was 0.70%.

Conclusion

Histological analysis of upper gastrointestinal biopsy specimens of the patients who presented with GERD symptoms revealed a number of well distinct clinicopathological entities. Oesophagitis which was the most prevalent condition associated with long standing reflux can be easily diagnosed endoscopically when associated with mucosal erosions. Histological evaluation plays an important role in the diagnosis of non-erosive reflux oesophagitis. The prevalence of Barrett disease has increased over the past decade, vastly related to improved screening facilities, better understanding and diagnosis of this condition and possibly due to an increase in incidence due to changes in the life style. The diagnosis of Barrett's should be based on the combination of careful endoscopic evaluation and histologic review of the biopsy material. In the presence of multiple, well established risk factors which include chronic GERD, older age (> 50 years), male sex, elevated body mass index, intra abdominal fat distribution and hiatal hernia, endoscopic screening for Barrett oesophagus is recommended. When compared, the population of patients with columnar cell metaplasia without goblet cells is much higher than the population of patients with goblet cell metaplasia. Regular surveillance of all of these patients will have a huge economic impact on the national health care system. Until there is scientific evidence to prove that columnar cell metaplasia without goblet cells is a risk factor for the development of oesophageal adenocarcinoma, it seems appropriate to hold back from labeling these patients with Barrett oesophagus [12, 13].

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