



Pathogenesis of acute gastroesophageal reflux disease might be changing

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Gastroesophageal reflux disease (GERD) is prevalent worldwide and its incidence is increasing as the obese population rises (1). Notably, in North America, Europe, the Middle East, and South America, the estimated prevalence of GERD is high and GERD in pediatric patients has recently become a significant problem.

The Genval Workshop, in their first consensus on GERD, defined this disease as the presence of esophageal mucosal breaks or the occurrence of reflux-induced symptoms severe enough to impair quality of life (2). For a long time, chemical injury of the esophageal mucosa by gastric acid was considered to be the major pathogenesis of GERD. Proton pump inhibitors (PPIs) are widely used to treat GERD and are believed to suppress gastric acid secretion and subsequent mucosal injury.

Although caustic chemical injury by gastric acid is certainly one of the most important factors of GERD occurrence, various other factors also correlate with the incidence of this disease, including the presence of a sliding hiatus hernia, low lower esophageal sphincter pressure, transient lower esophageal sphincter relaxation, an acid pocket, obesity, aging, increased distensibility of the esophagogastric junction, prolonged esophageal clearance, and delayed gastric emptying. Moreover, the severity of GERD symptoms is affected by factors such as the acidity of the refluxate, its proximal extent, the presence of gas in the refluxate, duodenal gastroesophageal reflux, longitudinal muscle contraction, mucosal integrity, and peripheral and central sensitization (3,4).

Basal cell hyperplasia, elongation of the connective tissue

papillae, spongiosis, infiltration of neutrophils, eosinophils, and lymphocytes, and the dilatation of capillaries are typical histological findings of GERD (5). It has been widely accepted that reflux esophagitis develops from a caustic, chemical injury that starts at the luminal surface of the squamous epithelium and progresses through the epithelium and lamina propria into the submucosa. The acid-induced death of surface cells is assumed to stimulate a proliferative response in the basal cells that renew the squamous epithelium. This has been presumed to result in hyperplasia of the basal cell layer and the papillae; these histologic findings are considered characteristic of reflux esophagitis. Finally, acid-induced epithelial injury and cell death are assumed to promote an inflammatory response, which is manifested histologically by inflammatory cells infiltrating the damaged squamous epithelium (6-8).

In 2009, Souza *et al.* reported an alternative hypothesis for the mechanism of GERD occurrence (9). Using a chemical burn rat model of esophageal mucosal injury, they clarified that reflux esophagitis started with lymphocytic infiltration into the submucosa, which progressed to the epithelial surface. They also reported that exposure of the squamous cells to acidified bile salts significantly increased the secretion of interleukin-8 (IL-8) and IL-1, which induced lymphatic infiltration. However, these results are documented only in the rat model. Certainly, it is difficult to confirm these histological changes over time using human biopsies.

In the current study, Dunbar *et al.* documented histological changes over time in patients with acute

GERD. Patients were originally diagnosed with LA grade C esophagitis and were successfully treated with PPIs. Before the start of this study, they confirmed endoscopically that the patients either had no findings of or only LA grade A esophagitis. On days 9 and 16, after PPIs were stopped, esophagoscopy and biopsy of the esophageal mucosa were performed. On day 16, all patients had endoscopic findings of reflux esophagitis. Pathological examination revealed that this acute GERD was a T lymphocyte-predominant form of inflammation with minimal involvement by neutrophils and eosinophils. Furthermore, esophageal basal cells and papillary hyperplasia developed in areas without surface erosions. These findings are compatible with the hypothesis by Souza *et al.* that the pathogenesis of GERD is not an acid injury of the esophageal epithelial surface, but instead is the lymphocytic infiltration of the submucosa induced by inflammatory cytokines (9).

To date, several studies documented the association of inflammatory cytokines or chemokines with GERD (10-12). In 2014, using human esophageal squamous cell lines, Huo *et al.* confirmed that acidic bile salt medium caused esophageal epithelial cells to express IL-8 mRNA and protein by activating the IL-8 promoter through nuclear factor-kappa B (NF- κ B) and activator protein 1 (AP-1) binding. In addition, omeprazole inhibits IL-8 expression through effects on NF- κ B and AP-1 that are entirely independent of the effects on gastric acid secretion (13).

The current study is clinically significant and meaningful because it is the first report to demonstrate the histological changes of reflux esophagitis over time in humans. It also shows the possibility that the alternative hypothesis for the pathogenesis of GERD occurrence may be correct. However, it can be argued whether or not the lymphocyte infiltration induced by inflammatory cytokines is the cause of acute GERD. All of the current patients had reflux esophagitis (LA grade A to C) 2 weeks after stopping PPIs. Mucosal surface injury by gastric acid might be an initiating event and the subsequent secreted inflammatory cytokines might be a secondary event that induces T lymphocyte infiltration. Regarding pathological findings in the two patients with no esophagitis 1 week after stopping PPIs (patient No. 8,9), references to pathological findings were not described. It is a significant finding whether these patients showed a T lymphocyte inflammation without epithelial surface injury.

We have a considerable concern regarding the pathological changes that occur the earlier periods after stopping PPIs. If T lymphocyte infiltration is confirmed

before esophagitis is endoscopically confirmed or before epithelial surface injury is pathologically indicated, the authors' claim that the pathogenesis of acute GERD may be the result of a cytokine-mediated response rather than the result of chemical injury is further strengthened.

As the authors commented, this study has several limitations. Patients originally had reflux esophagitis of LA grade C and were treated with PPIs. It is not clear that those populations are appropriate to investigate the general pathogenesis of acute GERD.

In conclusion, the current study is the first to document histological changes of the esophageal mucosa in human patients with acute GERD over time. This study also suggested a new concept of the pathogenesis of GERD based on the current histological and endoscopic findings. Further research in this field is needed; however, cytokine-mediated T lymphocyte-predominant esophageal inflammation may be recognized as a new pathogenesis of GERD.

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