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Progress in the Study of Esophageal Heterotopic Gastric Mucosa

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Abstract

Esophageal Heterotopic Gastric Mucosa (EHGM) refers to the abnormal growth of gastric mucosal tissue in the esophagus, which often appears endoscopically as a localized red-orange, island-like mucosa that is clearly demarcated from the surrounding esophageal mucosa. It is primarily detected during esophagogastroduodenoscopy (EGD), and although rare, cases of Barrett's esophagus and malignant tumors associated with EHGM have been reported. In this article, we review various studies on the relevance of different aspects of EHGM, including etiology and pathogenesis, epidemiology, symptoms and staging, diagnosis, acid secretion studies, tumor transformation, and treatment options.

Keywords

Esophagogastric Mucosal Ectasia, Diagnostic, Endoscopic Techniques, Research Progress

1. Introduction

The esophageal mucosa is typically lined with squamous epithelium, while the gastric mucosa consists of a single layer of columnar epithelium. When one or multiple regions of the esophageal mucosa are substituted by gastric mucosa, this condition is referred to as esophagogastric mucosal ectasia, also known as Esophageal Heterotopic Gastric Mucosa (EHGM). This mucosal lesion predominantly affects the proximal and distal esophagus, with infrequent occurrences in the mid-esophagus, earning it the additional names of esophageal inlet patch or cervical inlet patch (CIP) [1]. Cases of Barrett's esophagus and malignant tumors linked to EHGM have been documented. This review provides an overview of the current advancements in the study of esophagogastric mucosal ectasia.

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2. Etiology and Pathogenesis of EHGM

The etiology of Ectopic Heterotopic Gastric Mucosa (EHGM) remains a subject of debate among experts, with three primary academic theories. The prevailing view among scholars is that EHGM is a congenital developmental anomaly [2]. During fetal development, the esophageal squamous epithelium typically supplants the columnar epithelium. If this substitution is incomplete, remnants of the embryonic gastric mucosa may persist in the esophagus and gradually proliferate. The proximal and distal esophagus are the final regions to undergo this epithelial transition, hence the term EHGM. Wang, H [3], and colleagues were the first to document a case of ectopic gastric mucosa situated between the mucosal muscular layer and the submucosal layer at the esophago-gastric junction. Other academics propose that the development of EHGM is associated with acquired injuries to the esophageal mucosa, such as trauma, dietary factors, reflux, and infections. These can damage the esophageal squamous epithelium, prompting compensatory hyperplasia of the ectopic gastric mucosa to mend the injury, thus leading to its formation. A minority of scholars suggest that blockage of the proximal esophageal glands may result in retention cysts that, upon rupturing, could cause the presence of ectopic gastric mucosa [4].

3. Epidemiology

Various studies conducted both domestically in China and internationally have reported differing detection rates for esophagogastric mucosal ectasia, ranging from approximately 0.1% to 13.8% abroad [5], and between 0.25% to 1.26% in China. In reality, the prevalence of esophagogastric mucosal ectasia might be underreported, as past autopsy studies have indicated a prevalence as high as 70% [6]. The detection rate of esophagogastric mucosal ectasia is influenced by numerous factors, and the reasons behind this may be closely associated with advancements in gastroscopy techniques, innovations in gastroscopy modalities, and the endoscopist's level of experience.

4. Symptoms and Staging

The throat condition, unrelated to dysphagia, may paradoxically improve during meals, often leading to its oversight by clinicians. Reports indicate that ablating ectopic gastric mucosa in the proximal esophagus can alleviate dysphagia symptoms [7]. The histological subtypes of esophagogastric mucosal ectasia are primarily categorized into three groups: fundic, sinus, and body. A pathological study conducted by Xi J H *et al.* [8] revealed that the gastric fundus type is prevalent, while the non-gastric fundus type is relatively rare (approximately 30%). Symptoms predominantly arise from the acid-secreting function of the fundic glandular epithelium, and the ectopic gastric mucosa, being in close proximity to the larynx and pharynx, refluxes acid secretions, thereby causing associated symptoms. Excessive gastric acidity can also trigger chronic inflammation and ulceration, which may be severe enough to result in perforation. Based on symptoms and pathology, Von

et al. [9] established a clinicopathological classification system in 2004, which divides esophagogastric mucosal ectasia (EHGM) into five types: Type I exhibits no clinical symptoms, complications, or pathological changes; Type II presents with symptoms but no pathological changes; Type III involves both symptoms and pathological changes, along with benign complications; Type IV is characterized by rare abnormal proliferations, such as the development of intraepithelial neoplasms; and Type V is the most severe, potentially progressing to esophageal adenocarcinoma. Symptoms and corresponding treatments may vary based on several factors, including the type of ectopic mucosa, *Helicobacter pylori* colonization, and the presence of ectopic gastric mucosa outside the esophagus. However, further research is necessary to reach definitive conclusions.

5. Diagnosis

The diagnosis of esophagogastric mucosal ectasia is established through the utilization of endoscopy and pathological examination.

5.1. Diagnostic Endoscopy

1) General Endoscopy: Electronic white light gastroscopy plays a crucial role as a supplementary diagnostic tool for identifying gastroesophageal lesions in clinical practice and is now extensively utilized in the diagnosis and management of numerous conditions. Endoscopic entrance plaques predominantly occur in the cervical esophagus, frequently on the right posterior wall of the esophagus. They often present as singular or multiple lesions, which may be adjacent, circumferential, or interconnected. The morphology of these plaques can vary, appearing as islands, circles, ovals, or stripes, and their coloration ranges from orange to red. The surface may be flat, raised, or depressed. As technology advances, an increasing array of diagnostic techniques is being implemented.

2) Staining Endoscopy: Also known as pigment endoscopy, involves spraying Lugol's solution to distinguish lesions from the surrounding squamous epithelium. The principle is that the squamous epithelium of the esophagus contains glycogen and, when it encounters iodine in Lugol's solution, it presents a brownish change. However, the specificity of staining endoscopy is low.

3) Confocal Microendoscopy: A novel form of endoscopy, which eliminates the need for biopsy and histopathological examination, utilizes a confocal microscope embedded within the endoscope's tip. This technique enables the acquisition of high-resolution, high-magnification cross-sectional images at the cellular level of living tissues. It can distinctly identify abnormal structural morphology and clearly delineate the boundary between squamous and columnar cells. Consequently, it represents a more specific diagnostic method for evaluating EHGM.

4) Narrow Band Imaging (NBI): This innovative optical technique employs a narrow band filter to selectively remove the broad spectrum of red, blue, and green light waves. Leveraging the unique optical properties of blood within the mucosa, which absorbs blue and green light more readily, NBI enhances the contrast and

definition of the mucosal epithelium and submucosal blood vessels. These structures are distinctly outlined and exhibit a pronounced color distinction against the pale cyan hue of the healthy esophageal mucosa [10]. The surface of lesions appears either flattened and smooth or finely granular. NBI has become widely adopted in clinical settings.

5) Optical Coherence Tomography (OCT): OCT represents a novel optical diagnostic technique [11]. The imaging probe of OCT is introduced to the examination site via the endoscopic channel, enabling the acquisition of real-time, three-dimensional images of the intricate cross-sections of biological tissues. This method offers non-contact, non-invasive, and high-resolution tomographic imaging of the digestive tract, effectively revealing the cellular morphology and structural details of the tissues.

5.2. Pathological Diagnosis

In pathological examination, physicians inspect tissue samples to determine esophagogastric mucosal heterotopia, observing whether there is abnormal proliferation of gastric mucosal cells. These cells may exhibit characteristics of glands, mucus, and columnar cells. Pathological section microscopy aids in understanding the structure of the lesion area. The cytological characteristics of esophageal and gastric mucosa are different, and pathological testing can assist in diagnosis. Physicians also need to conduct a comprehensive assessment in conjunction with clinical symptoms and medical history. Slicing and microscopic examination help physicians clarify the lesion structure, providing a basis for treatment decisions.

6. Acid Secretion

The mucosa secretes gastric acid, leading to chronic inflammation, which is pivotal evidence for symptom development in patients with esophagogastric mucosal heterotopia (EHGM). Historically, J. W. Hamilton [12] and colleagues utilized Congo red dye for staining diseased mucosa during endoscopy and observed that the lesion area darkened upon stimulation with pentagastrin, indicating acid secretion. Nakajima [13] and his team also conducted endoscopic Congo red staining in EHGM patients to measure the pH at various points in the esophagus. They noted that the pH at the esophagogastric junction was around 5.6, which plummeted to 2.4 at the ectopic gastric mucosa. While some researchers argue that these studies merely confirm increased acid exposure in the esophagus and do not directly demonstrate acid secretion by the ectopic gastric mucosa, Kim EA [14] and others demonstrated through continuous 24-hour pH monitoring of an EHGM patient that the ectopic gastric mucosa of the cervical esophagus was indeed capable of acid secretion, with the upper esophagus pH being < 4, while no significant pH change was observed in the lower segment, indicating a dissociation phenomenon. In recent years, Kishimoto *et al.* [15] used 8-channel pH monitoring in a patient with rare gastric mucosal ectasia in the middle esophagus and found that sensors near the mid-segment region detected a postprandial acid phase (pH 3 -

4), whereas regions near the proximal and distal sensors remained neutral, further suggesting that the ectopic gastric mucosa can secrete acid. Acid secretion is also suspected to be a cause of malignant transformation, although the correlation between symptomatic acid-associated EHGM and reported cases of malignancy remains unclear.

7. Tumour Transformation

7.1. Barrett's Esophagus

In recent years, the detection rate of EHGM has exhibited an upward trend. The potential relationship between EHGM and Barrett's esophagus primarily revolves around several key aspects. Initially, the correlation of cellular origin is of interest. A study conducted by Lauwers GY *et al.* [16] revealed similar immunohistochemical features between the two conditions, including the expression of identical mucin core proteins and cytokeratin patterns, suggesting a homologous nature. In contrast, Feurle GE *et al.* [17] evaluated the immunohistology and determined that EHGM and Barrett's esophagus have distinct cellular origins, with EHGM arising from the embryonic stage of gastric mucosa and Barrett's esophagus cells originating from more primitive and multipotent gastrointestinal stem cells. Secondly, clinical manifestations and supplementary investigations are important considerations. Various studies have indicated similarities in clinical symptoms, 24-hour pH monitoring, and high-resolution esophageal manometry between EHGM and Barrett's esophagus. More recently, Khatri R *et al.* [18] conducted a retrospective analysis of endoscopic findings in 27,498 patients. Their study revealed that the prevalence of columnar-lined esophagus (CIP) was 1.3%, with 17.1% of these cases also having Barrett's esophagus. Conversely, the prevalence of Barrett's esophagus was 4.9%, and 4.6% of these cases had CIP. Patients with CIP alone presented symptoms similar to those with concurrent Barrett's esophagus. Functional esophageal examinations demonstrated decreased lower esophageal sphincter pressure and increased mean esophageal acid exposure time in both patient groups. In conclusion, the prevalence of Barrett's esophagus among patients with EHGM is notably high. A substantial number of studies have concurred that EHGM and Barrett's esophagus share certain similarities. The rising detection rate of EHGM offers a larger pool of samples for clinical research, and there is hope for significant advancements in the future.

7.2. *Helicobacter pylori*

Speculation regarding *Helicobacter pylori* (*H. pylori*, *HP*) and esophagogastric mucosal ectasia, as well as reflux, remains controversial. Some scholars propose that *H. pylori* colonization in the CIP [19] may be essential for reflux. However, conclusions about the correlation between *H. pylori* and the prevalence of GERD itself are inconsistent in the literature [20]. Additionally, since *H. pylori* resides in a distinct environment at the ectopic lesion in the esophagus compared to the stomach, this difference may lead to *H. pylori*'s inability to fully demonstrate its

activity and function, rendering it less pathogenic at that site rather than absolutely so. Most studies have indicated a correlation between the likelihood of *H. pylori* colonization within the EHGM and its density within the stomach. Nonetheless, Lin T [21] *et al.* reported isolated *H. pylori* colonization of ectopic gastric mucosa in patients with no abnormalities on routine laboratory investigations. Therefore, further relevant research is necessary.

7.3. Esophageal Cancer

The majority of esophageal cancers develop in the distal esophagus, where the middle and lower thirds predominantly consist of squamous cell carcinomas. In contrast, nearly all adenocarcinomas are found in the distal esophagus, a phenomenon largely attributed to the presence of gastro-esophageal reflux disease (GERD) and Barrett's esophagus. The incidence of adenocarcinoma resulting from esophagogastric mucosal ectasia (EHGM) has been reported to be 1.5% or less [22]. In recent years, Kitasaki, N. [23] *et al.* documented the first case of recurrent adenocarcinoma originating from EHGM, where the patient experienced two recurrences of adenocarcinoma at the same location over a 40-month span. This case underscores the significance of long-term surveillance for EHGM and suggests that esophagogastric mucosal ectasia may be a significant risk factor for proximal esophageal adenocarcinoma. Given the low prevalence of precancerous lesions in EHGM, routine biopsy to ascertain its histopathology is not typically recommended; rather, targeted biopsy should be contemplated when irregular areas are detected.

8. Treatment

Given the low incidence of esophagogastric mucosal ectasia, there is no universally accepted treatment protocol, and the majority of patients who are clinically asymptomatic do not necessitate interventional therapy. The management of esophagogastric mucosal ectasia (EHGM) can be categorized into four primary approaches: Firstly, observation and follow-up are appropriate for patients who are asymptomatic, have a small affected area, and lack related complications. In such cases, regular monitoring is sufficient. Secondly, pharmacological intervention is indicated when patients exhibit symptoms and there is a strong suspicion that these symptoms are attributable to EHGM. Acid suppression therapy, particularly using proton pump inhibitors (PPIs), is recommended as the initial treatment strategy [23]. Yamada T [24] and other researchers have corroborated the presence of proton pumps in the mucosa of symptomatic patients through immunohistochemical analysis. Thirdly, endoscopic treatment becomes a viable option for patients who do not respond to PPI therapy or present with signs of heterogeneous hyperplasia. This modality primarily includes radio frequency ablation (RFA), argon plasma coagulation (APC), endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD). Lastly, surgical intervention may be warranted in the event of severe complications that are not amenable to endoscopic treatment.

9. Summary

In summary, esophagogastric mucosal ectasia, recognized as a condition with significant clinical risk factors, poses a considerable threat to patients' daily lives and safety. Consequently, it is imperative to conduct thorough research into the disease's pathogenesis, clinical manifestations, and diagnostic and treatment methods. This will enable us to more effectively mitigate the risks associated with the condition and foster the efficient advancement of clinical research endeavors.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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