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## Issues and controversies in esophageal inlet patch

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### Abstract

The proximal esophagus is rarely examined, and its inspection is often inadequate. Optical chromoendoscopy techniques such as narrow band imaging improve the detection rate of inlet patches in the proximal esophagus, a region in which their prevalence is likely underestimated. Various studies have reported correlations between these esophageal marks with different issues such as Barrett's esophagus, but these findings remain controversial. Conflicting reports complicate the process of interpreting the clinical features of esophageal inlet patches and underestimate their importance. Unfortunately, the limited clinical data and statistical analyses make reaching any conclusions difficult. It is hypothesized that inlet patches are correlated with various esophageal and extraesophageal symptoms, diagnoses and the personalized therapeutic management of patients with inlet patches as well as the differential diagnosis for premalignant lesions or early cancers. Due to its potential underdiagnosis, there are no consensus guidelines for the management and follow up of inlet patches. This review focuses on questions that were raised from published literature on esophageal inlet patches in adults.

**Key words:** Inlet patch; Ectopic gastric mucosa; Heterotopic gastric mucosa; Esophageal cancer; Narrow band imaging; Optical chromoendoscopy; Cervical esophagus; Functional dyspepsia; Barrett's esophagus; *Helicobacter pylori*

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**Core tip:** Esophageal inlet patches were largely considered to be either asymptomatic or relatively unimportant. More recently, an increasing array of documented symptoms have been correlated with these esophageal lesions, which have made them a controversial subject. Presently, there are no standard guidelines for the management of

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symptomatic heterotopic gastric mucosa of the esophagus. Specifically, diagnosing the condition through the use of longer scope withdrawal times paired with the routine use of optical chromoendoscopy in the cervical esophagus could be useful for further exploring the significance of inlet patches.

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## INTRODUCTION

Esophageal inlet patches (IPs) are a well-circumscribed area of mucosa that is salmon-pink in color, variable in size, and oval, round or even geographically shaped. It is most frequently observed during endoscopic evaluations of the cervical esophagus. The patch may have either a smooth surface or a slightly raised or depressed surface with heaped margins. Rarely, the inlet may appear as a protrusive or polypoid lesion. Small lesions may be covered by the squamous epithelium and present without evident changes in the overlying esophageal mucosa<sup>[1-4]</sup>. Barrett's esophagus has been widely studied due to its association with adenocarcinoma and gastroesophageal reflux disease, while IPs, the "less popular relative" of esophageal intestinal metaplasia, were overlooked to an extent and their pathogenic role could be underestimated. Similar to Barrett's esophagus, IPs have often been described as both a congenital condition (the remnants of the columnar lining of the fetal esophagus) and as an acquired condition due, for example, to a metaplastic transformation resulting from chronic acid injury or ruptured cystic glands<sup>[5-7]</sup>. However, IP, which is also referred to as esophageal heterotopic gastric mucosa, remains a controversial topic. Heterotopic gastric mucosa has also been reported in other locations including the rectum and the anus as well as the duodenum, jejunum, gallbladder, cystic duct, and the ampulla of Vater<sup>[8]</sup>. Their etiology and pathological characteristics remain unexplored and unclear<sup>[8]</sup>. In addition to the gastric mucosa, other heterotopic tissues such as bronchial or pancreatic tissues may also occasionally be found in the esophagus and are typically reported in pediatric studies, which supports the hypothesis of congenital IPs<sup>[9]</sup>.

This review provides an up-to-date summary of the literature on esophageal IPs in adult populations and focuses on questions that have been raised in recently published articles. We then illustrate several ways that heterotopic mucosa might contribute to a range of digestive issues.

## IP - ESOPHAGEAL INCIDENTALOMA OR UNDERDIAGNOSED LESION

Are IPs an "incidentaloma" of the upper esophagus that can be identified while performing an endoscopy? Currently, most endoscopists consider esophageal heterotopic gastric mucosa to be a clinically irrelevant entity. Others performed small studies on IPs or submitted case reports with interesting yet varied results that provided isolated incidental findings rather than significant correlations<sup>[9,10]</sup>.

An early description of IP in the upper esophagus from a postmortem examination dates back to 1805<sup>[2,5]</sup>. In this report, it was described as an aberrant gastric fundus-type epithelium that was situated in the cervical esophagus.

Most instances of IPs consist of heterotopic columnar gastric mucosa that is often located just below the upper esophageal sphincter or in the postcricoid region of the esophagus<sup>[7]</sup>. Cases of similar lesions have been detected in the distal region of the esophagus as well<sup>[4,9]</sup>.

The previously reported prevalence of IPs in the proximal esophagus ranges from 0.18% to 14% in endoscopic studies<sup>[11]</sup>.

IP might not be as rare as it is described in some previous studies<sup>[3,5,12-14]</sup> because its incidence has been increased by attentive scope withdrawal and thorough inspection of the proximal mucosa as well as by using optical chromoendoscopy such as narrow band imaging (NBI) evaluations.

Moreover, autopsy reports show a significant incidence of up to 70%<sup>[9]</sup>.

Therefore, this discrepancy further demonstrates that the esophageal IP detection rates during endoscopies could be higher as the time spent withdrawing the scope increases and as the NBI mode is more frequently used. In most cases, the first part of the esophagus is blindly intubated and this region is then often neglected when withdrawing the scope.

IPs are often noticed and visualized during endoscopy procedures in patients who present with complaints of dyspepsia, typical or atypical symptoms of reflux disease or a persistent globus sensation. Other complaints associated with this lesion include an unexplained and persistent cough, hoarseness, odynophagia and dysphagia<sup>[15,16]</sup>. Furthermore, there is a variable prevalence of laryngopharyngeal reflux symptoms reported for this condition that ranges from 20% to 73.1%<sup>[7,15,17]</sup>, which can be largely explained by the susceptibility of the laryngopharyngeal mucosa to acid reflux that is produced by the ectopic gastric mucosa. Mucus secretion has also been taken into consideration<sup>[18]</sup> (Figure 1). Associations with chronic ear or sinus disease have also been reported<sup>[9]</sup>. In contrast, there are also authors who have found no association between IPs and the presence or absence of these upper esophageal symptoms in their patients<sup>[19,20]</sup>. In another recent study, despite a high prevalence of IPs (10.9% in 239 patients), the authors determined that there were no significant associations with any type of symptoms<sup>[21]</sup>.

In 2004, von Rahden *et al*<sup>[7]</sup> proposed a useful clinicopathologic classification for heterotopic gastric mucosa of the esophagus (Supplemental Table 1).

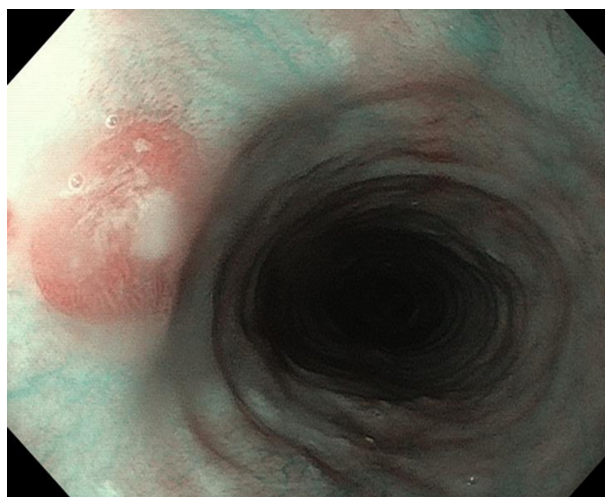
Interestingly, some studies have reported that esophageal IP is more common in men than in women<sup>[16,22]</sup>. If we take the distribution of symptoms into account, women are known to present more often with globus, for instance, which indicates that a higher incidence of symptomatic IPs might be expected in women. In our experience, we have noticed that there is an anxious profile for patients that present with inlets that is predominant in women and can appear as hypochondria. These patients would typically be classified as type-2 according to von Rahnen's classification system (Table 1). The most common symptom that we observed was a globus sensation without any size-dependent correlation. Similarly, other studies found that there was a female predominance in globus patients but, in contrast, concluded that it was related to reflux disease<sup>[23]</sup>. Regardless, they recorded important size-related information and showed that IPs with longer lengths and larger total areas were more common in globus patients than in non-globus patients.

## IPS AND NON-NEOPLASTIC SYNCHRONOUS LESIONS

The association of IPs with Barrett's esophagus (BE) and gastric lesions such as *Helicobacter pylori* (*H. Pylori*)-associated gastritis lesions has been debated across multiple studies<sup>[5]</sup>. The conflicting results on the association between IPs and BE<sup>[9,16]</sup> indicate that their interaction is largely speculative. However, a pathogenetic link between BE and IPs can be argued due to their immunohistological similarity, including the expression of the same mucin core protein and their cytokeratin patterns<sup>[24]</sup>. In contrast, Feurle *et al*<sup>[25]</sup>'s assessment of the neuroendocrine immunohistochemical staining patterns of IP and BE was that they are distinct parts of a spectrum of foregut differentiation, with IP representing the embryonic stage of gastric mucosa, while cells from BE represent more primitive and multipotent cells.

There is also controversy surrounding the speculated association of *H. pylori* with IP and reflux. Some authors hypothesized that reflux may be required for *H. pylori* to colonize in the IP<sup>[26]</sup>. However, there are discrepancies in the literature in the conclusions about the correlation between *H. Pylori* and the prevalence of gastroesophageal reflux disease (GERD) itself<sup>[27,28]</sup>. Other studies hypothesized that nonulcer dyspepsia, including globus sensation, is due to chronic inflammation produced by *H. pylori* in the gastric mucosa of the IP<sup>[8]</sup>. One case report in particular found that *H. pylori* eradication was able to ameliorate the extragastric symptoms associated with IPs and resulted in beneficial histopathological changes<sup>[29]</sup>, which suggests that *H. pylori* and *H. pylori*-eradication therapy might have different effects in patients with IP. However, this report was limited by the fact that the patient had both gastric and esophageal IP- *H. pylori* colonization. Thus, it is impossible to determine if the improvement in globus sensation and heartburn are due exclusively to the eradication of *H. pylori* or to the proton pump inhibitor (PPI) that is commonly included in the treatment as well (Figure 2).

The oxyntic mucosa cell type is most commonly reported<sup>[5,30]</sup> but cardiac, antral and mixed types (both oxyntic and antral) have also been detected<sup>[31,33]</sup>. The ectopic gastric mucosa of the IP has a high probability of *H. pylori* colonization, with a prevalence of



**Figure 1** A discreet area of flat salmon pink mucosa with mucus on surface typically found in the proximal esophagus of a 45-year-old anxious woman with globus sensation.

up to 82%<sup>[31]</sup>. However, this high percentage can be questioned if we consider that the detection of gastric *H. pylori* is thought to occur in the antral-type mucosa.

In contrast, another study found that the type of inlet mucosa did not influence the rate of *H. pylori* colonization<sup>[31]</sup> and found that *H. pylori* density and the type of mucosa were the only predictors for active inflammation in the IP and there was a higher chance of active inflammation in patients with active *H. PYLORI* infections in the nonoxyntic mucosa (antral or transitional) of the IP.

In 2010, Alagozlu *et al*<sup>[8]</sup> found that IPs were *H. pylori*-positive in 23.5% of patients with a higher colonization rate in female patients than in male patients ( $P < 0.05$ ), and further showed that globus sensation was a persistent symptom. Interestingly, this study found that *H. pylori* was most common in the fundic-type mucosa (81.2%) and that synchronous *H. pylori* I gastritis was present in all of the patients with an infection of the IP. The range of sizes was reported, from 5 to 32 mm and between 10% and 30% of the circumference of the proximal esophagus, but they did not determine if the increased colonization rate was size-dependent.

However, some reports have shown that the size of the patch can be symptom-related (*e.g.*, a correlation with dysphagia severity) and hypothesized that it could be a function of increased acid secretion<sup>[33]</sup> or due to stricture at the distal end of the IP<sup>[34]</sup>.

The majority of studies have found a correlation between the prevalence of *H. pylori* in IPs with their gastric density, which suggests that independent patch colonization is not possible<sup>[4]</sup>. However, the isolated colonization of IPs without the involvement of *H. pylori*-positive gastritis has recently been described as well<sup>[35]</sup>.

Fortunately, a five-year follow up of 20 patients with both cervical heterotopic gastric mucosa and *H. pylori* infection by Latos *et al*<sup>[36]</sup> did not find any malignant transformation, dysplasia or metaplasia. However, their study was potentially limited by a small patient population.

A retrospective analysis of a larger population found significant associations between IPs and male gender, globus sensation, dysphagia, upper respiratory complaints, BE and adenocarcinomas on BE<sup>[16]</sup>. Interestingly, there was no relationship between IPs and dysplasia or adenocarcinoma found in women.

In isolated cases, there are reports of complications that include bleeding, ulceration, strictures, perforation and tracheoesophageal fistulization, and subcutaneous abscesses<sup>[34,37]</sup>. In a small case series, the detection of an IP web or ring suggested the pathogenesis of an acid-induced lesion<sup>[38]</sup>. Importantly, colonization with *H. pylori* may exacerbate these complications<sup>[31,36]</sup>.

Other studies have also described cases of food impaction that were related to IP-associated strictures or rings<sup>[39-41]</sup>.

Concomitant findings of IPs in patients with inflammatory bowel disease, celiac disease, neurofibromatosis or blue rubber bleb nevus syndrome are likely to be incidental<sup>[42]</sup> (Figure 3).

Recently, an isolated case of eosinophilic gastritis was described with involvement of the polypoid esophageal gastric inlet and it was reported that the dysphagia and hoarseness was resolved after resection<sup>[43]</sup>. It should also be noted that the first reported case of an esophageal xanthoma in the cervical IP can likely be interpreted as a chronic injury of IP<sup>[44]</sup>.

**Table 1 Clinicopathologic classification of cervical heterotopic gastric mucosa (CHGM) proposed by von Rahden *et al*<sup>[7]</sup> and proposed management**

CHGM I	Asymptomatic individuals with esophageal CHGM- reassurance of the patient+ optional follow up
CHGM II without morphologic changes	Symptomatic individuals with esophageal CHGM (globus sensation, cough, hoarseness or "extraesophageal manifestations")- reassurance and explain to the patient possible implication such as esophageal hypersensitivity+ acid suppression, prokinetic+ select cases to exclude <i>H Pylori</i> if persistence of symptoms+ endoscopic reevaluation in case of suspected complication of inlet patch
CHGM III	Inlet patch complications- endoscopic therapy ( <i>e.g.</i> , dilatation, argon plasma coagulation, radiofrequency ablation)
CHGM IV	Dysplasia within the inlet patch- endoscopic management (EMR, ESD)+ surveillance
CHGM V	Invasive cancer within the inlet patch- interdisciplinary team decision (gastroenterologist- oncologist- surgeon)

## IP – CONGENITAL OR ACQUIRED LESION

The greater incidence of IPs in pediatric populations and the immunohistochemical studies that suggest an embryologic origin supports the theory that it is a congenital condition. During normal embryonic development, the squamous cell epithelium of the esophagus is replaced by columnar epithelium starting from the mid esophagus to the cervical esophagus. However, persistent columnar-lined areas that result from incomplete squamous epithelialization can further differentiate into an IP<sup>[14]</sup>. Interestingly, there is a lower prevalence reported in older populations, and some authors suggest that IPs may regress with age<sup>[10]</sup>. Moving past this dated theory, the hypothesis that long-term acid reflux can lead to the development of IPs with intestinal metaplasia in the upper esophagus<sup>[45]</sup> seems less credible because histology rarely shows any additional intestinal metaplasia on the IPs. Therefore, the inlet is likely congenital and can be predisposed to certain conditions due to its primary histology and then further influenced by other cumulative factors such as colonization with *H. pylori*, concomitant gastro-esophageal reflux disease (GERD) or BE.

We recommend that the association between IP and GERD should be studied in patients without synchronous BE. Moreover, care should be taken not to overestimate the association between IP and GERD due to upper acid reflux produced by the heterotopic gastric mucosa.

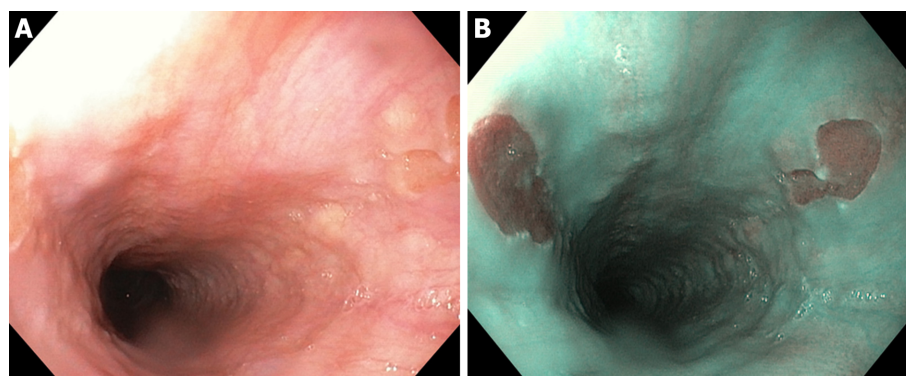
## IPS AND FUNCTIONAL DYSPESIA

Lesions in the cervical esophagus need to be recognized and addressed, especially in cases where there are no other lesions in the upper tract that can explain the patients' complaints, and these steps should be taken prior to establishing a diagnosis of functional dyspepsia or nonerosive reflux disease. Patients with a potential diagnosis of functional dyspepsia may be frustrated due to the lack of a known cause for their condition. This situation can lead to a vicious anxiogenic cycle. Furthermore, simply explaining to the patient that the likely harmless ectopic gastric mucosa in their esophagus could be causing their symptoms could lead to better management of their condition through the placebo effect. Psychological distress is common and the pathophysiology of persistent functional dyspepsia is not completely understood. However, in specific categories of patients, having discussions with the patient after identifying an IP and letting them know that it may be a congenital condition could help to reassure them, reach acceptance and reduce their symptomatic burden.

The persistent globus sensation may also originate from pressure applied to the upper esophageal sphincter stemming from an irritable IP condition or by the reflexive contraction of the upper esophageal sphincter due to a respiratory defense mechanism, likely related to reflux<sup>[46-48]</sup>.

We further hypothesize that *H. pylori* colonization or heterotopic gastric mucosa lead to alterations in cervical perception, which could also cause persistent symptoms.

Moreover, there has been substantial debate over synchronous motility disorders. Korkut *et al*<sup>[19]</sup> showed that there was esophageal motor dysfunction in some patients with IPs based on manometry and a 24 h dual-probe pH study, which may also be responsible for symptomatic patients without other digestive disorders. Rosztoczy *et al*<sup>[49]</sup> reported that prolonged acid exposure in both the cervical and distal esophagus,



**Figure 2** Double mirror flat inlet patches in (A) white light endoscopy vs (B) optical chromoendoscopy (narrow band imaging), in a middle age woman with *Helicobacter pylori*-associated gastritis and globus sensation ameliorated after the eradication therapy.

a longer biliary reflux exposure time in the distal esophagus, a prolonged relaxation and decreased peristaltic wave amplitude, and decreased lower esophageal sphincter pressure could be other factors that contribute to abnormal motility function in these patients.

Another study speculated that mucus secretion rather than acid production could be the cause of symptoms in patients with globus sensations that were unresponsive to PPI therapy<sup>[20]</sup>. In this small population of patients, histopathologic examinations revealed only the presence of cardiac mucosa.

## IPS AND ESOPHAGEAL CANCER

Another pertinent question is whether IPs are implicated in the pathophysiology of esophageal cancer. Taking into consideration the number of studies that report the IP as a harmless area of mucosa that can be overlooked, one might tend to think the limited number of cases with both esophageal cancer and IPs are coincidental.

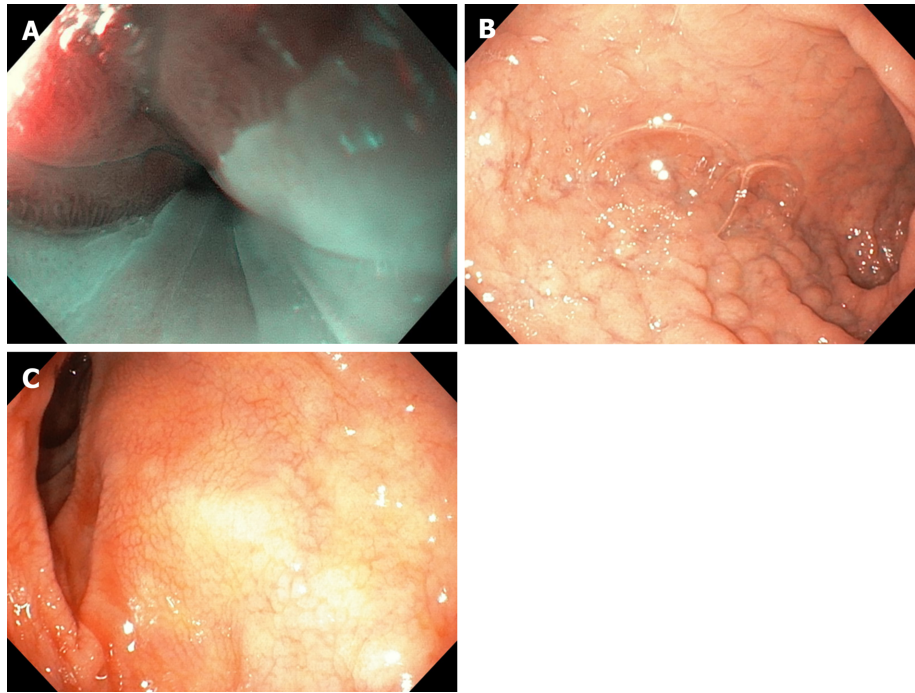
On the other hand, recent case reports on adenocarcinoma describe IPs that are small and flat lesions and fairly discernible from benign IPs<sup>[50,51]</sup>. Therefore, should endoscopists feel guilty for missing this kind of lesion or for not routinely obtaining biopsies? The answer to this question depends on the degree that the lesion is involved in the patient's symptoms and if the lesion impacts the patient's outcome.

Other concomitant risk factors must also be taken into consideration. A recent study<sup>[52]</sup> found no differences related to age, race, household income or waist-to-hip-ratio, while the patients with IPs had a heavier smoking history (mean 23.7 packs/year *vs* 16.3 packs/years,  $P = 0.006$ ). There was not a significant difference from those who never smoked. No association was found between weekly alcohol intake and IPs<sup>[52]</sup>. A recent report of a 14-year large population study that analyzed whether IPs are significantly associated with proximal esophageal adenocarcinomas revealed only 39 cases of simultaneous diagnoses from their literature review and only three additional cases during their study<sup>[14]</sup>. Indeed, the authors also mention that underreporting IPs during the endoscopy could be a potential limitation.

In 2013, Chong *et al*<sup>[9]</sup> could only find 43 cases of esophageal cancers in the literature that presented concomitantly with heterotopic gastric mucosa since 1950 when Carrie *et al*<sup>[53]</sup> reported the first case.

Furthermore, Sahin *et al* found no cases of adenocarcinoma or dysplasia and detected additional intestinal metaplasia in only five of 123 IP cases<sup>[30]</sup>.

The lack of studies with long-term follow-ups for IP might be a source of this bias. Other authors such as Peitz *et al*<sup>[11]</sup> have also considered that the prevalence of IPs is underestimated, making a correlation with advanced cervical esophageal cancer difficult. Due to the rare incidence of preneoplasia reported for IP, the authors do not support the routine biopsy to determine its histopathology, but rather targeted biopsies should be considered whenever any irregularities within the area are observed. In addition to this opinion, there are technical difficulties in typically occurring region located in upper esophagus (contractions of the upper esophageal sphincter or low tolerance of unsedated patients), so the routine biopsy should be limited to atypical locations of the IPs (*e.g.*, distal or middle part of the esophagus) or for atypical appearances (*e.g.*, polypoid types). For symptomatic patients with usually located IPs, and when confirmation is not possible by biopsy, a virtual chro-



**Figure 3** Concomitant findings of inlet patches in patients with inflammatory bowel disease, celiac disease, neurofibromatosis or blue rubber bleb nevus syndrome are likely to be incidental. A: Large inlet patch from 16 to 20 cm from the incisors in a young woman with globus sensation and concomitant celiac disease. The patient underwent an upper endoscopy because of persistent iron deficiency anemia. B: Nodular appearance of duodenal mucosa and C: flattened villi in the same patient.

moendoscopy with selected follow up cases could be helpful.

Confocal laser endomicroscopy could avoid both doctor and patient anticipatory anxiety related to a proper diagnosis. Unfortunately, this technique's feasibility for routine use is impaired by increased costs and limited access.

Detection of IP-like lesions and subsequent confirmation by histology would help to avoid confusing incipient cancers with heterotopic mucosa. IPs present with a reddish or salmon-rose colored focal area on standard endoscopy and as a homogeneous dark brown lesion that is distinctly separated from the light green squamous epithelium in the NBI mode<sup>[54]</sup>. NBI systems can be very helpful to identify brownish areas with brown dots and branching vessels in the cervical esophagus as potential superficial esophageal cancers. Therefore, the combined application of magnification and NBI can help to inform and direct the diagnostic management and early detection of esophageal neoplasia<sup>[55]</sup>. Magnifying endoscopy with the NBI system is superior to conventional white-light endoscopy for the detection of early cancers and helps to resolve the microvascular patterns of the superficial esophageal mucosa<sup>[56,57]</sup>. Ideally, a future implementation of an automatic detection system for early neoplasia similar to the automated computer algorithm developed for incipient neoplasia in BE that proposed by Fons van der Sommen *et al*<sup>[58]</sup> could be implemented (Figure 4).

Whether the IP increases the risk of esophageal carcinoma remains controversial. Acid secretion was also a suspected cause of malignant transformation<sup>[59]</sup>, but there is a discrepancy between the symptomatic acid-related IP prevalence and the rarely reported cases of malignization. There are likely other simultaneous risk factors that are involved. However, considering that cancers in IPs are typically reported as isolated cases<sup>[60-62]</sup>, the focus should remain on being able to accurately differentiate between harmless IPs and superficial malignancies. As white-light endoscopies may not reveal the abnormal features of early neoplasias, the routine use of virtual chromoendoscopy in the esophagus is justifiable. Underreporting the incidence of IPs by endoscopy must be avoided and future studies should be performed to reach more pertinent conclusions.

## MANAGEMENT AND SURVEILLANCE CONSIDERATIONS

There are no standardized guidelines for the management of IPs other than Von



**Figure 4** Multiple small focal areas round in shape of gastric tissue, one of them slightly raised, noted in the right lateral field, 10 cm from the incisors, in a young man presenting for unexplained upper dysphagia.

Rahden *et al.*'s clinicopathological classification system, which attempts to tailor management but is based on the limited body of literature<sup>[7,63]</sup>. A thorough interdisciplinary collaboration (otorhinolaryngologist, pneumologist, endocrinologist, gastroenterologist, and potentially a psychiatrist) should be developed to increase the efficacy of IP diagnosis in patients with unexplained extraesophageal symptoms.

Symptoms and their response to treatment may depend on a range of factors such as the type of heterotopic mucosa, *H. pylori* colonization and extraesophageal IP factors, but further studies are necessary to reach firm conclusions.

Going forward, the focus should remain on reassuring the patient and the routine use of virtual chromoendoscopy in the proximal region of the esophagus to direct the appropriate collection of biopsies from the IP-like mucosa. Another concern is whether surveillance is necessary after identifying an IP. Currently, and potentially due to its place as an underdiagnosed entity, there are no consensus guidelines for the management and follow up of IPs.

As there was no demonstrated association between the histopathology and clinical symptoms of the IP<sup>[59]</sup>, symptomatic patients should be treated and considered for endoscopic reevaluation when other complications of the heterotopic gastric mucosa are suspected<sup>[30]</sup>. In selected cases, such as patients who are at a high risk of neoplasia or patients who are symptomatic, elderly, or smokers<sup>[64]</sup>, the IP should be systematically evaluated and meticulously described with an endoscopic diagnosis and the patient should be considered for surveillance. Von Rahnen's classification used in conjunction with the NBI description could be included in the endoscopic report to improve awareness of any potential evolution of the lesion during the next evaluation.

When a follow up is scheduled, the patient can be offered sedation for the second evaluation to provide a better examination or more accurate biopsy sampling. A minimum of two biopsies should be performed depending of the size of the inlet mucosa. An uncomplicated IP suggests a similar therapeutic attitude to functional dyspepsia or to nonerosive reflux disease. A differential diagnosis is required to determine which patients will benefit from alternative strategies. Since independent acid secretion episodes are a likely symptomatic cause, PPI and/or antacids paired with psychological reassurance should be the initial treatment option for symptomatic patients. If patient anxiety is observed, a low dose anxiolytic can be included. Prokinetic agents may also help any abnormal local motility. Previous studies reported a significant reduction in the number of symptoms from patients on acid suppression therapy such as a PPI treatment<sup>[65-67]</sup>.

The duration of PPI administration is not clearly defined, but we have determined that therapy sessions such as "step-down" or "step-up" for 4-8 weeks, which are similar to GERD treatment, followed by on demand PPI can be effectively applied. If there are recurrences despite a high dose of PPI, adding H<sub>2</sub> receptor antagonists in the evening to the PPI in the morning can prevent the breakthrough of nocturnal acid secretion. Of course, future studies and more data are required to prove the efficacy of this strategy<sup>[68-71]</sup>. However, continuous and long-term use of both PPI and H<sub>2</sub> blockers should be discouraged to avoid developing resistances, rebound acid reflux and adverse effects. Long-term use of PPI also raises the question if it could influence the development of the heterotopic mucosa of the intestinal metaplasia or atrophy. Interestingly, one study reported that lesions were reduced in size after a course of

PPI 20 mg, twice daily<sup>[72]</sup>.

Similar gastric histological changes (inflammation, metaplasia, atrophy dysplasia and even adenocarcinoma of the IP with *H. pylori* colonization) have been reported<sup>[9]</sup>. Although there are insufficient data to recommend testing and eradicating *H. pylori* infections among patients with laryngopharyngeal reflux<sup>[73]</sup>, we suggest that the endoscopist should consider searching for cervical IPs. Then, a rapid urease test from the IP can be considered to determine the presence of *H. pylori* in patients with an unexplained persistent globus sensation or a dyspepsia despite the PPI treatment and without *H. pylori*-positive gastritis, or to decide to pursue further treatment in patients with persistent dyspepsia after previous gastric *H. pylori* eradication. In both the stomach and ectopic mucosa with *H. pylori* infections, eradication issues could also be taken into consideration such as different antibiotic susceptibilities and resistances.

In symptomatic patients with the typical aspects of IPs who are unresponsive to PPI, endoscopic therapy, such as argon plasma coagulation or radiofrequency ablation, have also been reported to be safe and effective<sup>[34,74]</sup>. However, in our opinion, the clinical management should be kept as noninvasive as possible so long as there are no unfavorable outcomes, complications or any suspicion of neoplasia. Endoscopic treatment is not only technically challenging due to the typical position of the IP in the proximal esophagus, but may also only be available in dedicated centers.

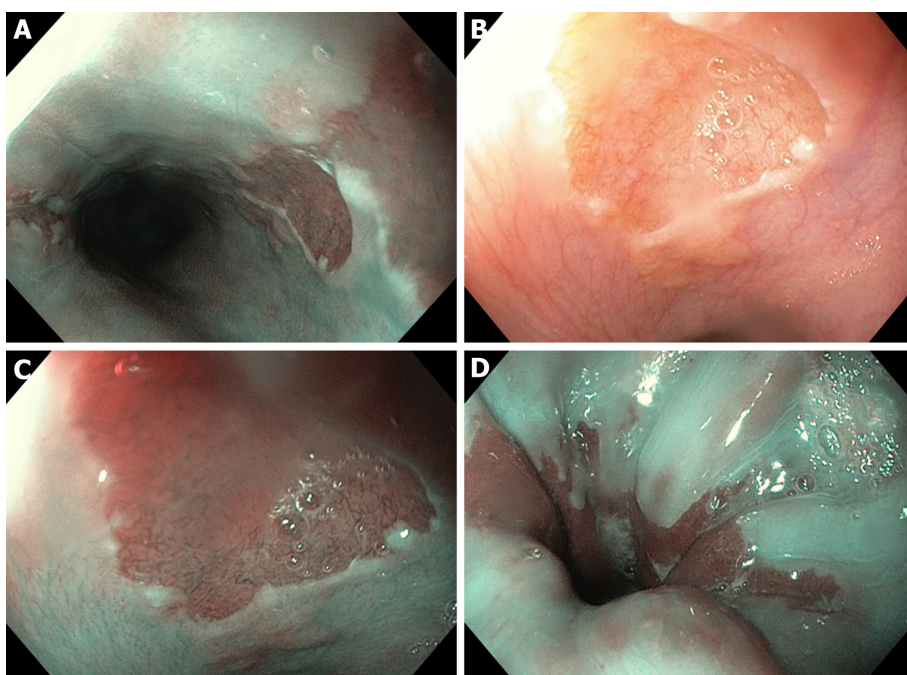
Strictures and webs can be managed by serial dilatation and biopsied to rule out malignancy<sup>[7,33]</sup>. A high-dose PPI paired with endoscopic thermal coagulation led to long-term amelioration of dysphagia in one case of IP with stricture and even to the recovery of the mucosa with normal squamous epithelium<sup>[75]</sup>. Endoscopic mucosectomy (EMR), argon plasma coagulation (APC) or surgical resection has also been used to successfully treat IP dysplasia or incipient neoplasia<sup>[7,15,74,76,77]</sup>, although the routine use of these strategies in this context has not been studied.

Other issues such as elevated surfaces<sup>[78]</sup> or the size of the IP should be taken into consideration before deciding which strategy is most appropriate. For instance, experts generally did not include patients with large IPs in the previously conducted interventional APC trials to exclude the possibility of stricture formation<sup>[18,79-81]</sup>. Furthermore, large areas of resected tissue and multiple lesions were independent predictors of stricture formation<sup>[82]</sup> (Figure 5).

In contrast, Kristo *et al*<sup>[78]</sup> recently reported an 80% rate of complete macroscopic and histologic eradication after 2 sessions of radiofrequency ablation with improvements in globus sensation and quality of life without any major adverse events or stricture formation after an approximate 2-year follow-up. The involvement of the esophageal heterotopic mucosa in esophageal pathology may eventually become as popular as BE, which will promote novel technologies such as hybrid-APC that could improve the therapeutic intervention for selected cases of large IPs in the future<sup>[83,84]</sup>. Confocal laser endomicroscopy could enable *in vivo* examinations of histology for flat lesions in the cervical esophagus in order to avoid a number of unnecessary biopsies and to direct any further EMR or endoscopic submucosal dissections<sup>[85]</sup>.

## CONCLUSION

The IP entity pendulates between being ignored, being underexplored, and being a source of curiosity. Its natural history and clinical significance are not yet well established due to the limited number of ambiguous studies in the literature. Unfortunately, the role of the esophageal heterotopic mucosa in various symptoms remains poorly understood and mainly based on speculation, while its sex-related prevalence remains to be calculated. We recommend the routine and careful examination of the cervical esophagus in developing the differential diagnosis, especially in patients who initially present with functional dyspepsia and in patients with upper dysphagia, chronic cough of unknown cause or persistent globus sensation. The malignization of IPs and its association with other entities such as Barrett's esophagus remains controversial. However, high-resolution magnifying endoscopes combined with optical chromoendoscopy such as NBI allows for the accurate differentiation between IPs and early flat neoplasias due to suggestive patterns.



**Figure 5** A: Three areas of cervical inlet patches, with kissing distribution, in a middle age women with uterine cancer history, presenting for reflux complaints and globus sensation. Detailed image in (B) white light endoscopy and (C) narrow band imaging. D: Irregular Z line in the same patient suggesting concomitant gastroesophageal reflux disease.

## REFERENCES

- 1 **Raine CH.** Ectopic gastric mucosa in the upper esophagus as a cause of dysphagia. *Ann Otol Rhinol Laryngol* 1983; **92**: 65-66 [PMID: 6824282 DOI: 10.1177/000348948309200115]
- 2 **Truong LD, Stroehlein JR, McKechnie JC.** Gastric heterotopia of the proximal esophagus: a report of four cases detected by endoscopy and review of literature. *Am J Gastroenterol* 1986; **81**: 1162-1166 [PMID: 3788924]
- 3 **Akbayir N, Alkim C, Erdem L, Sökmen HM, Sungun A, Başak T, Turgut S, Mungan Z.** Heterotopic gastric mucosa in the cervical esophagus (inlet patch): endoscopic prevalence, histological and clinical characteristics. *J Gastroenterol Hepatol* 2004; **19**: 891-896 [PMID: 15242492 DOI: 10.1111/j.1440-1746.2004.03474.x]
- 4 **Borhan-Manesh F, Farnum JB.** Incidence of heterotopic gastric mucosa in the upper oesophagus. *Gut* 1991; **32**: 968-972 [PMID: 1916499 DOI: 10.1136/gut.32.9.968]
- 5 **Tang P, McKinley MJ, Sporrer M, Kahn E.** Inlet patch: prevalence, histologic type, and association with esophagitis, Barrett esophagus, and antritis. *Arch Pathol Lab Med* 2004; **128**: 444-447 [PMID: 15043461 DOI: 10.1043/1543-2165(2004)128<444:IPHTA>2.0.CO;2]
- 6 **Avidan B, Sonnenberg A, Chejfec G, Schnell TG, Sontag SJ.** Is there a link between cervical inlet patch and Barrett's esophagus? *Gastrointest Endosc* 2001; **53**: 717-721 [PMID: 11375577 DOI: 10.1067/mge.2001.114782]
- 7 **von Rahden BH, Stein HJ, Becker K, Liebermann-Meffert D, Siewert JR.** Heterotopic gastric mucosa of the esophagus: literature-review and proposal of a clinicopathologic classification. *Am J Gastroenterol* 2004; **99**: 543-551 [PMID: 15056100 DOI: 10.1111/j.1572-0241.2004.04082.x]
- 8 **Alagozlu H, Simsek Z, Unal S, Cindoruk M, Dumlu S, Dursun A.** Is there an association between *Helicobacter pylori* in the inlet patch and globus sensation? *World J Gastroenterol* 2010; **16**: 42-47 [PMID: 20039447 DOI: 10.3748/wjg.v16.i1.42]
- 9 **Chong VH.** Clinical significance of heterotopic gastric mucosal patch of the proximal esophagus. *World J Gastroenterol* 2013; **19**: 331-338 [PMID: 23372354 DOI: 10.3748/wjg.v19.i3.331]
- 10 **Jabbari M, Goresky CA, Lough J, Yaffe C, Daly D, Côté C.** The inlet patch: heterotopic gastric mucosa in the upper esophagus. *Gastroenterology* 1985; **89**: 352-356 [PMID: 4007426 DOI: 10.1016/0016-5085(85)90336-1]
- 11 **Peitz U, Vieth M, Evert M, Arand J, Roessner A, Malfertheiner P.** The prevalence of gastric heterotopia of the proximal esophagus is underestimated, but preneoplasia is rare - correlation with Barrett's esophagus. *BMC Gastroenterol* 2017; **17**: 87 [PMID: 28701149 DOI: 10.1186/s12876-017-0644-3]
- 12 **Maconi G, Pace F, Vago L, Carsana L, Bargiggia S, Bianchi Porro G.** Prevalence and clinical features of heterotopic gastric mucosa in the upper oesophagus (inlet patch). *Eur J Gastroenterol Hepatol* 2000; **12**: 745-749 [PMID: 10929900 DOI: 10.1097/00042737-200012070-00005]
- 13 **Januszewicz W, Pietrzak A, Lenarcik M, Mróz A, Reguła J.** Long esophageal inlet patch as a rare cause of laryngopharyngeal symptoms. *Endoscopy* 2018; **50**: E61-E62 [PMID: 29245163 DOI: 10.1055/s-0043-123823]
- 14 **Orosey M, Amin M, Cappell MS.** A 14-Year Study of 398 Esophageal Adenocarcinomas Diagnosed Among 156,256 EGDs Performed at Two Large Hospitals: An Inlet Patch Is Proposed as a Significant Risk Factor for Proximal Esophageal Adenocarcinoma. *Dig Dis Sci* 2018; **63**: 452-465 [PMID: 29249048 DOI: 10.1007/s10620-017-4878-2]
- 15 **Jacobs E, Dehou MF.** Heterotopic gastric mucosa in the upper esophagus: a prospective study of 33 cases

- and review of literature. *Endoscopy* 1997; **29**: 710-715 [PMID: 9427488 DOI: 10.1055/s-2007-1004294]
- 16 **Neumann WL**, Luján GM, Genta RM. Gastric heterotopia in the proximal oesophagus ("inlet patch"): Association with adenocarcinomas arising in Barrett mucosa. *Dig Liver Dis* 2012; **44**: 292-296 [PMID: 22222950 DOI: 10.1016/j.dld.2011.11.008]
  - 17 **Chong VH**, Jaliha A. Heterotopic gastric mucosal patch of the esophagus is associated with higher prevalence of laryngopharyngeal reflux symptoms. *Eur Arch Otorhinolaryngol* 2010; **267**: 1793-1799 [PMID: 20437050 DOI: 10.1007/s00405-010-1259-2]
  - 18 **Bajbouj M**, Becker V, Eckel F, Miehke S, Pech O, Prinz C, Schmid RM, Meining A. Argon plasma coagulation of cervical heterotopic gastric mucosa as an alternative treatment for globus sensations. *Gastroenterology* 2009; **137**: 440-444 [PMID: 19410576 DOI: 10.1053/j.gastro.2009.04.053]
  - 19 **Korkut E**, Bektaş M, Alkan M, Ustün Y, Meco C, Ozden A, Soykan I. Esophageal motility and 24-h pH profiles of patients with heterotopic gastric mucosa in the cervical esophagus. *Eur J Intern Med* 2010; **21**: 21-24 [PMID: 20122608 DOI: 10.1016/j.ejim.2009.10.009]
  - 20 **Weickert U**, Wolf A, Schröder C, Autschbach F, Vollmer H. Frequency, histopathological findings, and clinical significance of cervical heterotopic gastric mucosa (gastric inlet patch): a prospective study in 300 patients. *Dis Esophagus* 2011; **24**: 63-68 [PMID: 20626446 DOI: 10.1111/j.1442-2050.2010.01091.x]
  - 21 **López-Colombo A**, Jiménez-Toxqui M, Gogearcoechea-Guillén PD, Meléndez-Mena D, Morales-Hernández ER, Montiel-Jarquín AJ, Amaro-Balderas E. Prevalence of esophageal inlet patch and clinical characteristics of the patients. *Rev Gastroenterol Mex* 2018 [PMID: 30318401]
  - 22 **Takeji H**, Ueno J, Nishitani H. Ectopic gastric mucosa in the upper esophagus: prevalence and radiologic findings. *AJR Am J Roentgenol* 1995; **164**: 901-904 [PMID: 7726045 DOI: 10.2214/ajr.164.4.7726045]
  - 23 **Hori K**, Kim Y, Sakurai J, Watari J, Tomita T, Oshima T, Kondo C, Matsumoto T, Miwa H. Non-erosive reflux disease rather than cervical inlet patch involves globus. *J Gastroenterol* 2010; **45**: 1138-1145 [PMID: 20582442 DOI: 10.1007/s00535-010-0275-8]
  - 24 **Lauwers GY**, Mino M, Ban S, Forcione D, Eatherton DE, Shimizu M, Sevestre H. Cytokeratins 7 and 20 and mucin core protein expression in esophageal cervical inlet patch. *Am J Surg Pathol* 2005; **29**: 437-442 [PMID: 15767795 DOI: 10.1097/01.pas.0000155155.46434.da]
  - 25 **Feurle GE**, Helmstaedter V, Buehring A, Bettendorf U, Eckardt VF. Distinct immunohistochemical findings in columnar epithelium of esophageal inlet patch and of Barrett's esophagus. *Dig Dis Sci* 1990; **35**: 86-92 [PMID: 2295298 DOI: 10.1007/BF01537228]
  - 26 **Wlaź J**, Mądro A, Kaźmierak W, Celiński K, Słomka M. Pancreatic and gastric heterotopy in the gastrointestinal tract. *Postepy Hig Med Dosw (Online)* 2014; **68**: 1069-1075 [PMID: 25228515 DOI: 10.5604/17322693.1119720]
  - 27 **Polat FR**, Polat S. The effect of *Helicobacter pylori* on gastroesophageal reflux disease. *JSLS* 2012; **16**: 260-263 [PMID: 23477175 DOI: 10.4293/108680812X13427982376860]
  - 28 **Ghoshal UC**, Chourasia D. Gastroesophageal Reflux Disease and *Helicobacter pylori*: What May Be the Relationship? *J Neurogastroenterol Motil* 2010; **16**: 243-250 [PMID: 20680162 DOI: 10.5056/jnm.2010.16.3.243]
  - 29 **Wüppenhorst N**, Viebahn B, Theile A, Radü HJ, Kist M. Culture and successful eradication of *Helicobacter pylori* from heterotopic gastric mucosa. *Z Gastroenterol* 2012; **50**: 677-679 [PMID: 22760679 DOI: 10.1055/s-0031-1299382]
  - 30 **Sahin G**, Adas G, Koc B, Akcakaya A, Dogan Y, Goksel S, Yalcin O. Is cervical inlet patch important clinical problem? *Int J Biomed Sci* 2014; **10**: 129-135 [PMID: 25018682]
  - 31 **Gutierrez O**, Akamatsu T, Cardona H, Graham DY, El-Zimaity HM. *Helicobacter pylori* and heterotopic gastric mucosa in the upper esophagus (the inlet patch). *Am J Gastroenterol* 2003; **98**: 1266-1270 [PMID: 12818267 DOI: 10.1111/j.1572-0241.2003.07488.x]
  - 32 **Akbayir N**, Sökmen HM, Çaliş AB, Bölükbaş C, Erdem L, Alkim C, Sakiz D, Mungan Z. Heterotopic gastric mucosa in the cervical esophagus: could this play a role in the pathogenesis of laryngopharyngeal reflux in a subgroup of patients with posterior laryngitis? *Scand J Gastroenterol* 2005; **40**: 1149-1156 [PMID: 16265772]
  - 33 **Behrens C**, Yen PP. Esophageal inlet patch. *Radiol Res Pract* 2011; **2011**: 460890 [PMID: 22091379 DOI: 10.1155/2011/460890]
  - 34 **Shimamura Y**, Winer S, Marcon N. A Giant Circumferential Inlet Patch With Acid Secretion Causing Stricture. *Clin Gastroenterol Hepatol* 2017; **15**: A22-A23 [PMID: 27729241 DOI: 10.1016/j.cgh.2016.10.004]
  - 35 **Lin T**, Linn S, Ona MA, Duddempudi S. *Helicobacter pylori*-positive inlet patch without concurrent *Helicobacter pylori* gastritis: case report of a patient with sleeve gastrectomy. *Ann Gastroenterol* 2017; **30**: 251 [PMID: 28243049 DOI: 10.20524/aog.2016.0102]
  - 36 **Latos W**, Sieroń-Stołtny K, Kawczyk-Krupka A, Operchalski T, Cieślak G, Kwiatek S, Bugaj AM, Sieroń A. Clinical evaluation of twenty cases of heterotopic gastric mucosa of upper esophagus during five-year observation, using gastroscopy in combination with histopathological and microbiological analysis of biopsies. *Contemp Oncol (Pozn)* 2013; **17**: 171-175 [PMID: 23788986 DOI: 10.5114/wo.2013.34376]
  - 37 **Katsanos KH**, Christodoulou DK, Kamina S, Maria K, Lambri E, Theodorou S, Tsampoulas K, Vasiliki M, Tsianos EV. Diagnosis and endoscopic treatment of esophago-bronchial fistula due to gastric heterotopy. *World J Gastrointest Endosc* 2010; **2**: 138-142 [PMID: 21160729 DOI: 10.4253/wjge.v2.i4.138]
  - 38 **Ainley EJ**. High oesophageal web formation in association with heterotopic gastric mucosa (the gastric inlet patch): a small case series. *Frontline Gastroenterol* 2011; **2**: 117-123 [PMID: 28839593 DOI: 10.1136/fg.2010.002311]
  - 39 **Guider J**, Scott L. Esophageal Rings and Stricture Related to a Circumferential Inlet Patch. *ACG Case Rep J* 2016; **3**: e124 [PMID: 27807576 DOI: 10.14309/crj.2016.97]
  - 40 **Rogart JN**, Siddiqui UD. Inlet patch presenting with food impaction caused by peptic stricture. *Clin Gastroenterol Hepatol* 2007; **5**: e35-e36 [PMID: 17683992 DOI: 10.1016/j.cgh.2007.05.025]
  - 41 **Yarborough CS**, McLane RC. Stricture related to an inlet patch of the esophagus. *Am J Gastroenterol* 1993; **88**: 275-276 [PMID: 8424433]
  - 42 **Rodríguez-Martínez A**, Salazar-Quero JC, Tutau-Gómez C, Espín-Jaime B, Rubio-Murillo M, Pizarro-Martín A. Heterotopic gastric mucosa of the proximal oesophagus (inlet patch): endoscopic prevalence, histological and clinical characteristics in paediatric patients. *Eur J Gastroenterol Hepatol* 2014; **26**: 1139-1145 [PMID: 25099680 DOI: 10.1097/MEG.0000000000000177]
  - 43 **Forcione DG**, Lauwers GY, Garber JJ. Eosinophilic gastritis with involvement of esophageal gastric inlet patch. *Gastrointest Endosc* 2018; **87**: 1356-1358 [PMID: 29108982 DOI: 10.1016/j.gie.2017.10.020]

- 44 **Hamada K**, Yamasaki Y, Kubota J, Okada H. Gastrointestinal: The first report of an esophageal xanthoma in the cervical inlet patch. *J Gastroenterol Hepatol* 2018; **33**: 1938 [PMID: 30084136 DOI: 10.1111/jgh.14386]
- 45 **Zhou C**, Kirtane T, Tsai TH, Lee HC, Adler DC, Schmitt JM, Huang Q, Fujimoto JG, Mashimo H. Cervical inlet patch-optical coherence tomography imaging and clinical significance. *World J Gastroenterol* 2012; **18**: 2502-2510 [PMID: 22654447 DOI: 10.3748/wjg.v18.i20.2502]
- 46 **Kwiatk MA**, Mirza F, Kahrilas PJ, Pandolfino JE. Hyperdynamic upper esophageal sphincter pressure: a manometric observation in patients reporting globus sensation. *Am J Gastroenterol* 2009; **104**: 289-298 [PMID: 19174789 DOI: 10.1038/ajg.2008.150]
- 47 **Corso MJ**, Pursnani KG, Mohiuddin MA, Gideon RM, Castell JA, Katzka DA, Katz PO, Castell DO. Globus sensation is associated with hypertensive upper esophageal sphincter but not with gastroesophageal reflux. *Dig Dis Sci* 1998; **43**: 1513-1517 [PMID: 9690388 DOI: 10.1023/A:1018862814873]
- 48 **Tokashiki R**, Funato N, Suzuki M. Globus sensation and increased upper esophageal sphincter pressure with distal esophageal acid perfusion. *Eur Arch Otorhinolaryngol* 2010; **267**: 737-741 [PMID: 19882344 DOI: 10.1007/s00405-009-1134-1]
- 49 **Rosztóczy A**, Izbéki F, Németh IB, Dulic S, Vadász K, Róka R, Gecse K, Gyökéres T, Lázár G, Tiszlavicz L, Wittmann T. Detailed esophageal function and morphological analysis shows high prevalence of gastroesophageal reflux disease and Barrett's esophagus in patients with cervical inlet patch. *Dis Esophagus* 2012; **25**: 498-504 [PMID: 22107367 DOI: 10.1111/j.1442-2050.2011.01281.x]
- 50 **Probst A**, Schaller T, Messmann H. Adenocarcinoma arising from ectopic gastric mucosa in an esophageal inlet patch: treatment by endoscopic submucosal dissection. *Endoscopy* 2015; **47** Suppl 1 UCTN: E337-E338 [PMID: 26134434 DOI: 10.1055/s-0034-1392423]
- 51 **Möschler O**, Vieth M, Müller MK. Endoscopic resection of an adenocarcinoma occurring in ectopic gastric mucosa within the proximal esophagus. *Endoscopy* 2014; **46** Suppl 1 UCTN: E24-E25 [PMID: 24523165 DOI: 10.1055/s-0033-1358807]
- 52 **Govani SM**, Metko V, Rubenstein JH. Prevalence and risk factors for heterotopic gastric mucosa of the upper esophagus among men undergoing routine screening colonoscopy. *Dis Esophagus* 2015; **28**: 442-447 [PMID: 24758607 DOI: 10.1111/dote.12221]
- 53 **CARRIE A**. Adenocarcinoma of the upper end of the oesophagus arising from ectopic gastric epithelium. *Br J Surg* 1950; **37**: 474 [PMID: 15414304 DOI: 10.1002/bjs.18003714810]
- 54 **Yamada T**, Tsuji A, Onoue S, Kaneko M, Tanioka F, Osawa S, Saido Y. Acid suppressive therapy improved symptoms due to circumferential cervical inlet patch with proton pumps (H<sup>+</sup>/K<sup>+</sup>-ATPase). *World J Clin Cases* 2017; **5**: 403-406 [PMID: 29204429 DOI: 10.12998/wjcc.v5.i11.403]
- 55 **Kawada K**, Kawano T, Sugimoto T, Yamaguchi K, Kawamura Y, Matsui T, Okuda M, Ogo T, Kume Y, Nakajima Y, Mora A, Okada T, Hoshino A, Tokairin Y, Nakajima Y, Okada R, Kiyokawa Y, Nomura F, Asakage T, Shimoda R, Ito T. Case of Superficial Cancer Located at the Pharyngoesophageal Junction Which Was Dissected by Endoscopic Laryngopharyngeal Surgery Combined with Endoscopic Submucosal Dissection. *Case Rep Otolaryngol* 2017; **2017**: 1341059 [PMID: 28154766 DOI: 10.1155/2017/1341059]
- 56 **Yoshida T**, Inoue H, Usui S, Satodate H, Fukami N, Kudo SE. Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. *Gastrointest Endosc* 2004; **59**: 288-295 [PMID: 14745410 DOI: 10.1016/S0016-5107(03)02532-X]
- 57 **Inoue H**, Kaga M, Ikeda H, Sato C, Sato H, Minami H, Santi EG, Hayee B, Eleftheriadis N. Magnification endoscopy in esophageal squamous cell carcinoma: a review of the intrapapillary capillary loop classification. *Ann Gastroenterol* 2015; **28**: 41-48 [PMID: 25608626]
- 58 **van der Sommen F**, Zinger S, Curvers WL, Bisschops R, Pech O, Weusten BL, Bergman JJ, de With PH, Schoon EJ. Computer-aided detection of early neoplastic lesions in Barrett's esophagus. *Endoscopy* 2016; **48**: 617-624 [PMID: 27100718 DOI: 10.1055/s-0042-105284]
- 59 **Kadota T**, Fujii S, Oono Y, Imajoh M, Yano T, Kaneko K. Adenocarcinoma arising from heterotopic gastric mucosa in the cervical esophagus and upper thoracic esophagus: two case reports and literature review. *Expert Rev Gastroenterol Hepatol* 2016; **10**: 405-414 [PMID: 26610162 DOI: 10.1586/17474124.2016.1125780]
- 60 **Abe T**, Hosokawa M, Kusumi T, Kusano M, Hokari K, Kagaya H, Watanabe A, Fujita M, Sasaki S. Adenocarcinoma arising from ectopic gastric mucosa in the cervical esophagus. *Am J Clin Oncol* 2004; **27**: 644-645 [PMID: 15577449 DOI: 10.1097/01.coc.0000147808.63442.b5]
- 61 **Alrawi SJ**, Winston J, Tan D, Gibbs J, Loree TR, Hicks W, Rigual N, Loré JM. Primary adenocarcinoma of cervical esophagus. *J Exp Clin Cancer Res* 2005; **24**: 325-330 [PMID: 16110768]
- 62 **Noguchi T**, Takeno S, Takahashi Y, Sato T, Uchida Y, Yokoyama S. Primary adenocarcinoma of the cervical esophagus arising from heterotopic gastric mucosa. *J Gastroenterol* 2001; **36**: 704-709 [PMID: 11686482]
- 63 **Georges A**, Coopman S, Rebeuh J, Molitor G, Rebouissoux L, Dabadie A, Kalach N, Lachaux A, Michaud L. Inlet patch: clinical presentation and outcome in children. *J Pediatr Gastroenterol Nutr* 2011; **52**: 419-423 [PMID: 21240021 DOI: 10.1097/MPG.0b013e3181f2a913]
- 64 **Akanuma N**, Hoshino I, Akutsu Y, Shuto K, Shiratori T, Kono T, Uesato M, Sato A, Isozaki Y, Maruyama T, Takeshita N, Matsubara H. Primary esophageal adenocarcinoma arising from heterotopic gastric mucosa: report of a case. *Surg Today* 2013; **43**: 446-451 [PMID: 22706784 DOI: 10.1007/s00595-012-0206-9]
- 65 **Kim EA**, Kang DH, Cho HS, Park DK, Kim YK, Park HC, Kim JH. Acid secretion from a heterotopic gastric mucosa in the upper esophagus demonstrated by dual probe 24-hour ambulatory pH monitoring. *Korean J Intern Med* 2001; **16**: 14-17 [PMID: 11417299 DOI: 10.3904/kjim.2001.16.1.14]
- 66 **Silvers WS**, Levine JS, Poole JA, Naar E, Weber RW. Inlet patch of gastric mucosa in upper esophagus causing chronic cough and vocal cord dysfunction. *Ann Allergy Asthma Immunol* 2006; **96**: 112-115 [PMID: 16440542 DOI: 10.1016/S1081-1206(10)61049-6]
- 67 **Hamilton JW**, Thune RG, Morrissey JF. Symptomatic ectopic gastric epithelium of the cervical esophagus. Demonstration of acid production with Congo red. *Dig Dis Sci* 1986; **31**: 337-342 [PMID: 3956328]
- 68 **Jeon HK**, Kim GH. Can Nocturnal Acid-breakthrough Be Reduced by Long-acting Proton Pump Inhibitors? *J Neurogastroenterol Motil* 2017; **23**: 145-148 [PMID: 28372039 DOI: 10.5056/jnm17037]
- 69 **Peghini PL**, Katz PO, Castell DO. Ranitidine controls nocturnal gastric acid breakthrough on omeprazole: a controlled study in normal subjects. *Gastroenterology* 1998; **115**: 1335-1339 [PMID: 9834259]
- 70 **Wang Y**, Pan T, Wang Q, Guo Z. Additional bedtime H2-receptor antagonist for the control of nocturnal

- gastric acid breakthrough. *Cochrane Database Syst Rev* 2009; CD004275 [PMID: [19821323](#) DOI: [10.1002/14651858.CD004275.pub3](#)]
- 71 **Katz PO**, Tutuian R. Histamine receptor antagonists, proton pump inhibitors and their combination in the treatment of gastro-oesophageal reflux disease. *Best Pract Res Clin Gastroenterol* 2001; **15**: 371-384 [PMID: [11403533](#) DOI: [10.1053/bega.2001.0185](#)]
  - 72 **Chong VH**, Jaliha A. Cervical inlet patch: case series and literature review. *South Med J* 2006; **99**: 865-869 [PMID: [16929882](#) DOI: [10.1097/01.smj.0000231246.28273.b0](#)]
  - 73 **Campbell R**, Kilty SJ, Hutton B, Bonaparte JP. The Role of Helicobacter pylori in Laryngopharyngeal Reflux. *Otolaryngol Head Neck Surg* 2017; **156**: 255-262 [PMID: [27803078](#) DOI: [10.1177/0194599816676052](#)]
  - 74 **Dunn JM**, Sui G, Anggiansah A, Wong T. Radiofrequency ablation of symptomatic cervical inlet patch using a through-the-scope device: a pilot study. *Gastrointest Endosc* 2016; **84**: 1022-1026.e2 [PMID: [27373671](#) DOI: [10.1016/j.gie.2016.06.037](#)]
  - 75 **McBride MA**, Vanagunas AA, Breshnahan JP, Barch DB. Combined endoscopic thermal electrocoagulation with high dose omeprazole therapy in complicated heterotopic gastric mucosa of the esophagus. *Am J Gastroenterol* 1995; **90**: 2029-2031 [PMID: [7485016](#)]
  - 76 **Sauvé G**, Croué A, Denez B, Boyer J. High-grade dysplasia in heterotopic gastric mucosa in the upper esophagus after radiotherapy: successful eradication 2 years after endoscopic treatment by argon plasma coagulation. *Endoscopy* 2001; **33**: 732 [PMID: [11490394](#) DOI: [10.1055/s-2001-16221](#)]
  - 77 **Pech O**, May A, Gossner L, Rabenstein T, Ell C. Management of pre-malignant and malignant lesions by endoscopic resection. *Best Pract Res Clin Gastroenterol* 2004; **18**: 61-76 [PMID: [15123085](#) DOI: [10.1016/S1521-6918\(03\)00104-5](#)]
  - 78 **Kristo I**, Rieder E, Paireder M, Schwameis K, Jomrich G, Dolak W, Parzefall T, Riegler M, Asari R, Schoppmann SF. Radiofrequency ablation in patients with large cervical heterotopic gastric mucosa and globus sensation: Closing the treatment gap. *Dig Endosc* 2018; **30**: 212-218 [PMID: [28884487](#) DOI: [10.1111/den.12959](#)]
  - 79 **Manner H**, May A, Miehlke S, Dertinger S, Wigglinghaus B, Schimming W, Krämer W, Niemann G, Stolte M, Ell C. Ablation of nonneoplastic Barrett's mucosa using argon plasma coagulation with concomitant esomeprazole therapy (APBANEX): a prospective multicenter evaluation. *Am J Gastroenterol* 2006; **101**: 1762-1769 [PMID: [16817835](#) DOI: [10.1111/j.1572-0241.2006.00709.x](#)]
  - 80 **Klare P**, Meining A, von Delius S, Wolf P, Konukiewicz B, Schmid RM, Bajbouj M. Argon plasma coagulation of gastric inlet patches for the treatment of globus sensation: it is an effective therapy in the long term. *Digestion* 2013; **88**: 165-171 [PMID: [24157960](#) DOI: [10.1159/000355274](#)]
  - 81 **Meining A**, Bajbouj M, Preeg M, Reichenberger J, Kassem AM, Huber W, Brockmeyer SJ, Hannig C, Höfler H, Prinz C, Schmid RM. Argon plasma ablation of gastric inlet patches in the cervical esophagus may alleviate globus sensation: a pilot trial. *Endoscopy* 2006; **38**: 566-570 [PMID: [16802267](#) DOI: [10.1055/s-2006-925362](#)]
  - 82 **Qumseya B**, Panossian AM, Rizk C, Cangemi D, Wolfsen C, Raimondo M, Woodward T, Wallace MB, Wolfsen H. Predictors of esophageal stricture formation post endoscopic mucosal resection. *Clin Endosc* 2014; **47**: 155-161 [PMID: [24765598](#) DOI: [10.5946/ce.2014.47.2.155](#)]
  - 83 **Kristo I**, Asari R, Rieder E, Riegler V, Schoppmann SF. Treatment of Barrett's esophagus: update on new endoscopic surgical modalities. *Minerva Chir* 2015; **70**: 107-118 [PMID: [25645114](#)]
  - 84 **Manner H**, May A, Kouti I, Pech O, Vieth M, Ell C. Efficacy and safety of Hybrid-APC for the ablation of Barrett's esophagus. *Surg Endosc* 2016; **30**: 1364-1370 [PMID: [26104794](#) DOI: [10.1007/s00464-015-4336-1](#)]
  - 85 **Prueksapanich P**, Pittayanon R, Rerknimitr R, Wisedopas N, Kullavanijaya P. Value of probe-based confocal laser endomicroscopy (pCLE) and dual focus narrow-band imaging (dNBI) in diagnosing early squamous cell neoplasms in esophageal Lugol's voiding lesions. *Endosc Int Open* 2015; **3**: E281-E288 [PMID: [26356321](#) DOI: [10.1055/s-0034-1391903](#)]



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