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Heterotopic Gastric Mucosal Patch of the Proximal Esophagus

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1. Introduction

Heterotopic gastric mucosa (HGM) is abnormally placed gastric mucosa outside of the stomach and can be found almost anywhere within the gastrointestinal tract (von Rahden et al., 2004). HGM is most commonly found in the esophagus. The most widely known HGM in the gastrointestinal tract is in the Meckel's diverticulum. However, HGM is also found in the other part of the gastrointestinal tract including the tongue (Melato & Ferlito, 1975; Ortiz, 1982; Surana, 1993), duodenum (Kibria et al., 2009; Mann, 2000), gallbladder (Hayama et al., 2010; Popkharitoy et al., 2008), jejunum (Boybeyi et al., 2008; Nowak & Deppisch, 1998), ileum (Chan et al., 1999; Erez et al., 1991), rectum (Garmendia et al., 2007; Vieth et al., 2005) and anus (Steele et al., 2004). Interestingly, HGM of the umbilicus, a part of remnant alimentary tract has also been report (Heo et al., 2010).

HGM patch (HGMP) of the proximal esophagus, also referred to as cervical inlet patch (CIP) is typically found in the proximal esophagus. It can also be found in the other part of the esophagus (Borhan-Manesh & Franum, 1991; Katsanos et al., 2010). On endoscopy, HGMP/CIP is clearly distinct from the esophageal squamous mucosa. HGMP/CIP is widely considered to be congenital in nature. However, it has also been proposed to be an acquired condition (Avidan et al., 2001; Meining & Baubouj, 2010). In clinical practice, HGMP/CIP is an under-recognized condition. The incidence reported in the literature varies with lower estimates in the earlier endoscopic studies (von Rahden et al., 2004). Later studies reported higher incidence (Ohara, 2010). The highest incidence was reported in an autopsy study (von Rahden et al., 2004). Use of newer endoscopic modalities has been reported to increase the pick up rates of HGMP/CIP.

HGMP/CIP is largely asymptomatic and is incidental findings during endoscopy evaluations for other gastrointestinal complaints. Commonly reported symptoms are those symptoms complex referred to as extra-esophageal manifestations of gastro-esophageal reflux disorders. Other common upper aero-digestive disorders have also been linked to HGMP/CIP. Despite the benign nature of HGMP/CIP, serious and important complications have been reported (von Rahden et al., 2004). Furthermore, associations with higher frequencies of laryngopharyngeal malignancies have also been reported (Basseri et al., 2009). A clinico-pathologic classification has been proposed which categorized HGMP/CIP into five distinct groups based on clinical, endoscopic and histological findings (von Rahden et

al., 2004). The management strategies of HGMP/CIP are not well defined and are dependent on the severity of symptoms. However, other newer treatment modalities have also been reported.

This chapter discusses the pathogenesis, the endoscopic features, clinical symptoms and the management of HGMP/CIP, an entity that is still under-recognised and is frequently missed during upper gastrointestinal endoscopy examinations.

2. Pathogenesis

HGMP is widely considered to be congenital in nature, as result of incomplete esophageal squamous epithelization during the embryogenic development stage (von Rahden et al., 2004). Reports of HGMP in the esophagus of young children and even babies support this theory (Boybeyi et al., 2008; Georges et al., 2011; Macha et al., 2005; Surana et al., 1993). However, it has also been proposed to be acquired in nature, similar to Barrett's esophagus (Avidan et al., 2001; Lauwers et al., 2005). There are based on similarities in the mucin and staining characteristics with CK7 and CK20 (Bogomoletz et al., 1988; Lauwers et al., 2005) between Barrett's esophagus and HGMP/CIP. Reports of higher incidence of Barrett's esophagus in patients with HGMP/CIP also suggested a link. Some has even proposed that the origins of HGMP/CIP may be different, congenital in children and acquired in adult (Lauwers et al., 2005). A recently proposed hypothesis suggested that HGMP/CIP developed from rupture retention cyst of the proximal esophagus (Meining & Baubouj, 2010).

2.1 Origin of heterotopic gastric mucosal patch of the proximal esophagus

2.1.1 Congenital origin theory

Embryogenesis of the esophagus

The development of the esophagus starts at the beginning of embryogenesis (Lieberman-Meffert et al., 2002). The upper aerodigestive tract (oro, naso and laryngopharynx), respiratory tract, esophagus and stomach and duodenum arise from the same embryogenic segment. The stages of development are correlated with the length of the embryo. At 3 mm crown-rump length, the esophagus is mainly lined with columnar mucosa and during development at 110 CR length (equivalent to 24 weeks gestation), the squamous lining begin to replace the columnar lining starting at the mid esophagus, migrating in both directions. The cervical region of the esophagus is the last area to get stratification and this account for the common findings of HGMP in the proximal esophagus. The embryogenic development of the esophagus is shown in Figure 1.

2.1.2 Acquired origins theories

Metaplastic transformation of squamous mucosa to columnar mucosa from chronic acid injury

It has also been proposed that the HGMP/CIP is an acquired condition as result of chronic inflammation from exposure to acid as part of gastroesophageal reflux disorders (Avidan et al., 2001; Lauwers et al., 2005). It is postulated that chronic acid exposure results in inflammation that leads to reactivation or proliferation of remnant columnar mucosa. These remnants columnar mucosa are present as microscopic foci in the esophageal lining or are covered by squamous mucosa. With chronic irritations, these foci develop into larger patch resulting in the formation of island of columnar mucosa, HGMP (Figure 2).

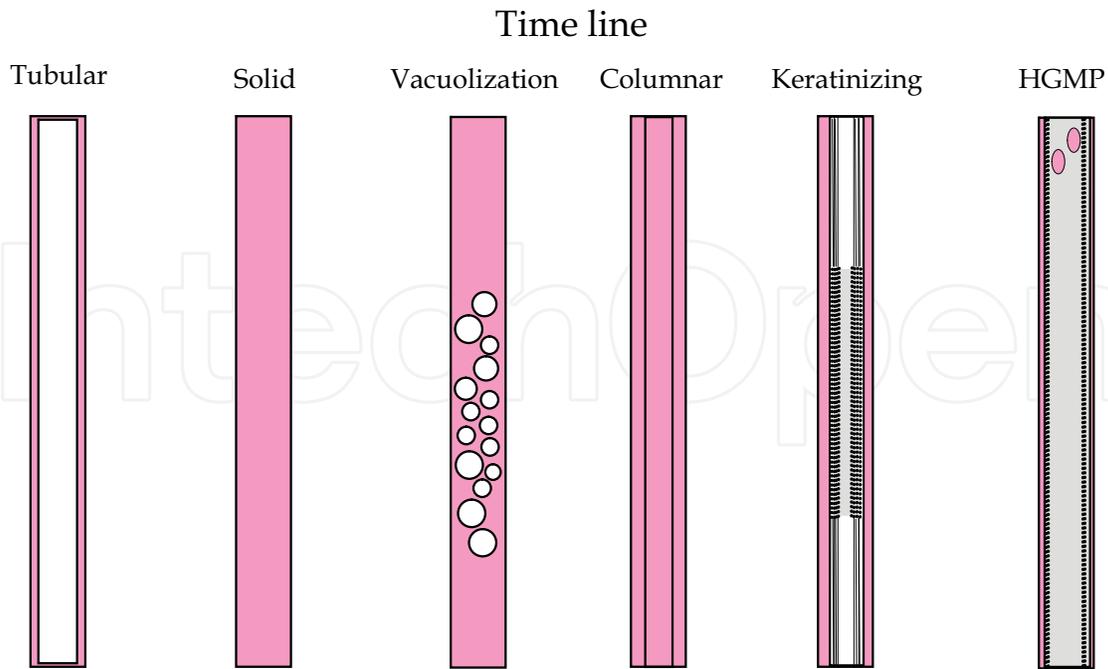


Fig. 1. Embryogenesis of the esophagus: solidification of the hollow tubular esophagus occur with rapid cellular proliferation followed by vacuoles formations (recanalization), columnarization (cilia phase shaded rippled pink) and the final stage of squamous cell mucosa formation (keratinizing followed by dekeratinizing phase-shaded gray). HGMP form when the final phase is incomplete

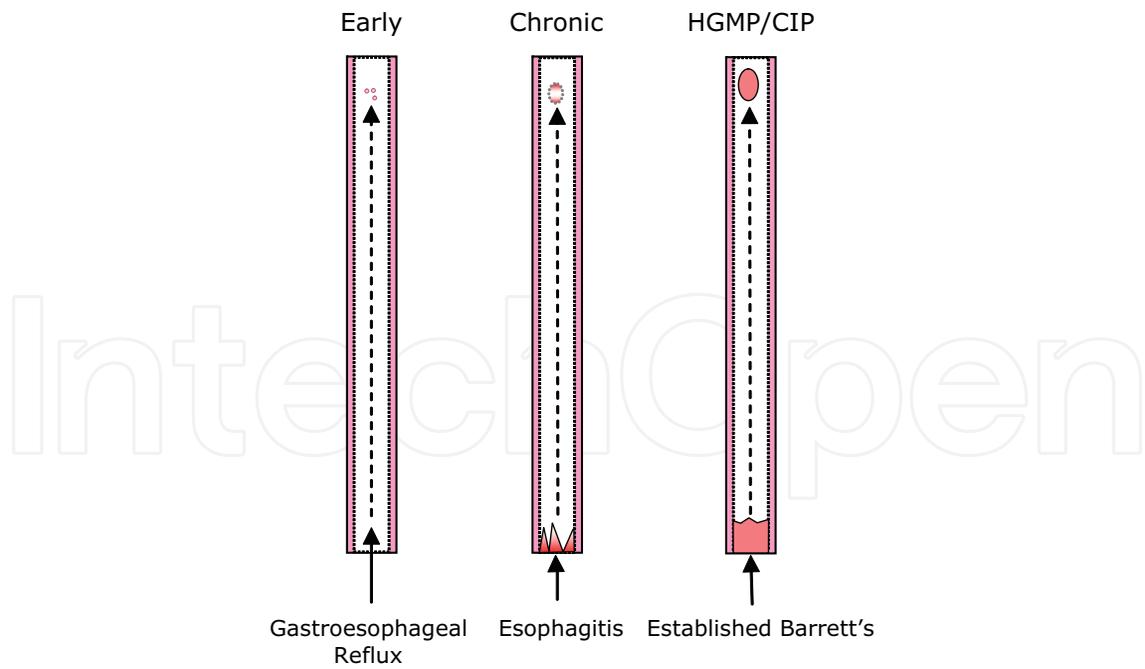


Fig. 2. Proposed acquired pathway through chronic reflux injury: Chronic acid (+/- pepsin and bile injury) leads to reflux esophagitis and reflux may reach the proximal esophagus resulting in similar changes. Chronic esophagitis leads to adaptive changes resulting in metaplasia metaplasia of the distal esophagus. Chronic injury in the proximal esophagus lead to reactivation of buried columnar cells resulting in formation of HGMP

Formation from ruptured retention cyst of the proximal esophagus

This proposed theory suggested that HGMP/CIP formed from ruptured proximal esophageal glandular retention cysts (Meining & Baubouj, 2010). The initial process starts with occlusion of esophageal glands in the proximal esophagus resulting in formation of retention cysts which is internally covered by columnar epithelium. With further enlargement of the cysts, they eventually rupture resulting in the formation of HGMP (Figure 3).

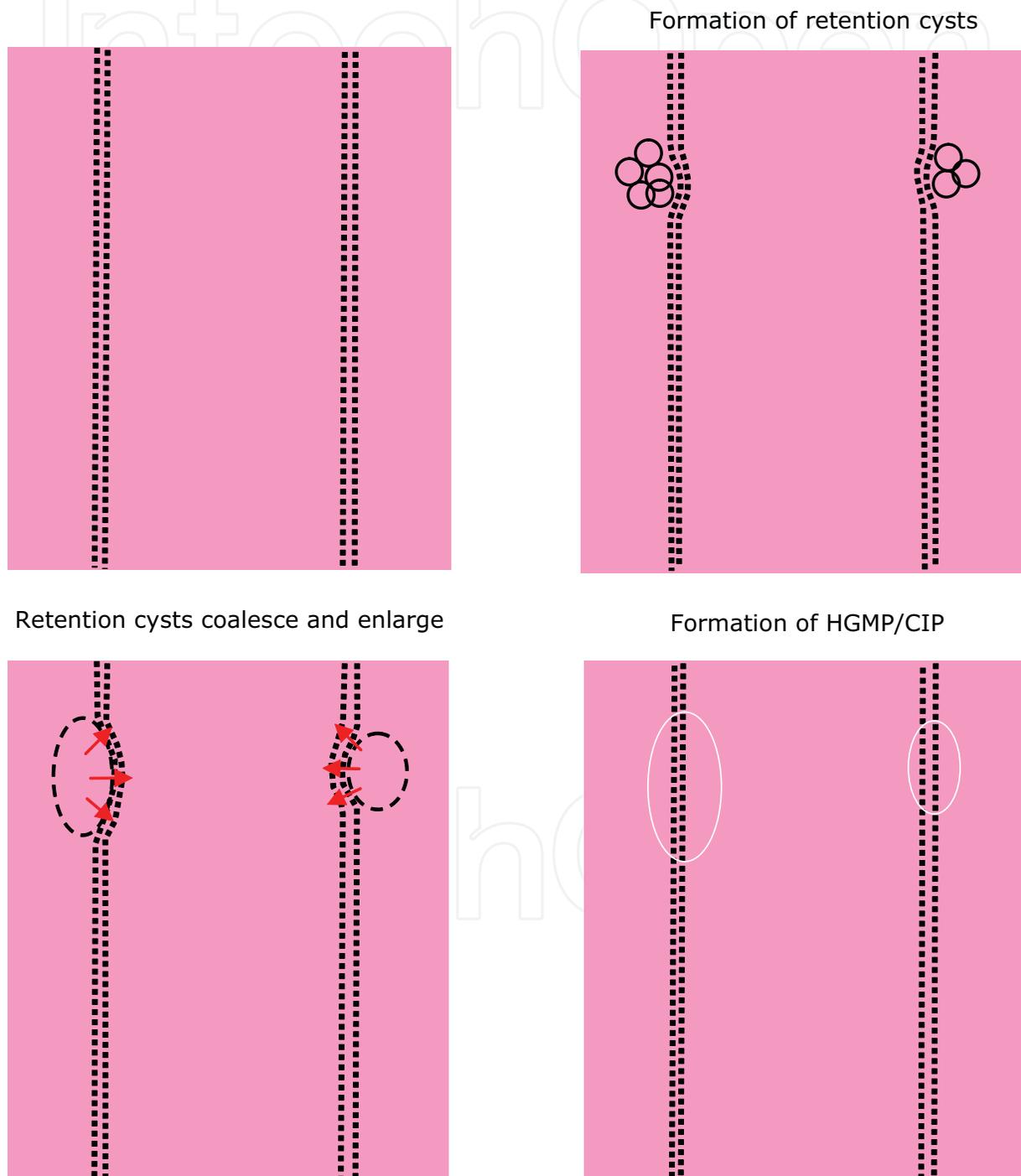


Fig. 3. Proposed acquired pathway through rupture of esophageal glandular retention cysts in the proximal esophagus

2.1.3 Others

Others have proposed that development of HGMP/CIP in adult and children may be different based on differences in the mucin protein (MUC) staining. It has been suggested that two pathogenetic pathways maybe involved: focal upper esophageal mucosal misdevelopment in pediatric population and patchy metaplastic replacement of squamous mucosa in adults with gastroesophageal reflux disease. (Lauwers et al., 2005)

3. Histology

HGMP/CIP consists of columnar mucosa found in the stomach (Figure 4). HGMP/CIP can contain glandular mucosa of different types similar to those found in the stomach. One study showed that the body or fundus mucosa type parietal cells is the most common accounting for 50 to 65% with the antral type and mixed transition type accounting for 20 to 25% respectively (Borhan-Manesh & Franum, 1991). Presence of acid producing parietal mucosa have been associated with acid production (Galan et al., 1998; Hamilton et al., 1986; Korkut et al., 2010; Yüksel et al., 2008). Mucin is also secreted (Bajbouj et al., 2009; Bogomoletz et al., 1988). The cytokeratin staining pattern of HGMP/CIP is similar to those seen with Barrett's esophagus with surface epithelium staining for CK7 and CK20 (Figure 5). The staining pattern of the esophagus and stomach is shown in Figure 6 (Latchford et al., 2001).

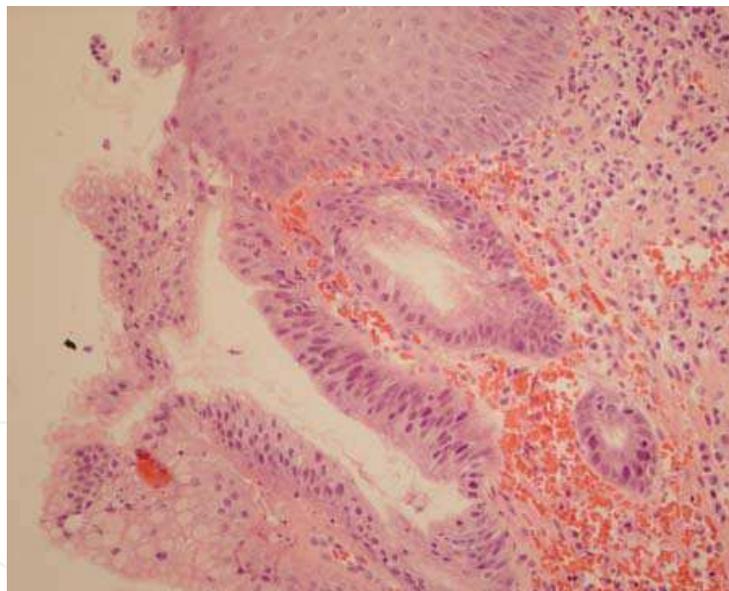


Fig. 4. High power view showing boundary between squamous esophageal mucosa and the glandular mucosa of the HGMP/CIP

Apart from CK, only one study had assessed the MUC protein profiles (Lauwers et al., 2005). This study showed that MUC5AC was strongly expressed on the surface and pits but not in the glands of HGMP/CIP and antral mucosa. In contrast, MUC5AC positivity was noted on the surface, pits and the glands of Barrett's esophagus. MUC6 similarly decorated the glands of HGMP/CIP and Barrett's esophagus. MUC2 was expressed rarely in HGMP/CIP with goblet cells but conspicuously on the surface and pits of Barrett's esophagus. MUC5B was seen in both HGMP/CIP and Barrett's esophagus and rarely in

the antral mucosa. The authors concluded that the similarities between HGMP/CIP and Barrett's esophagus but not with normal antral mucosa fit with the hypothesis that both lesions may originate from sub-mucosal esophageal mucous glands. Despite this, there are differences seen between HGMP/CIP and Barrett's esophagus. Staining pattern was also different between HGMP/CIP and the embryogenic esophagus. The authors of this study suggested that HGMP/CIP etiology may be different, congenital in children or babies and acquired in adult.

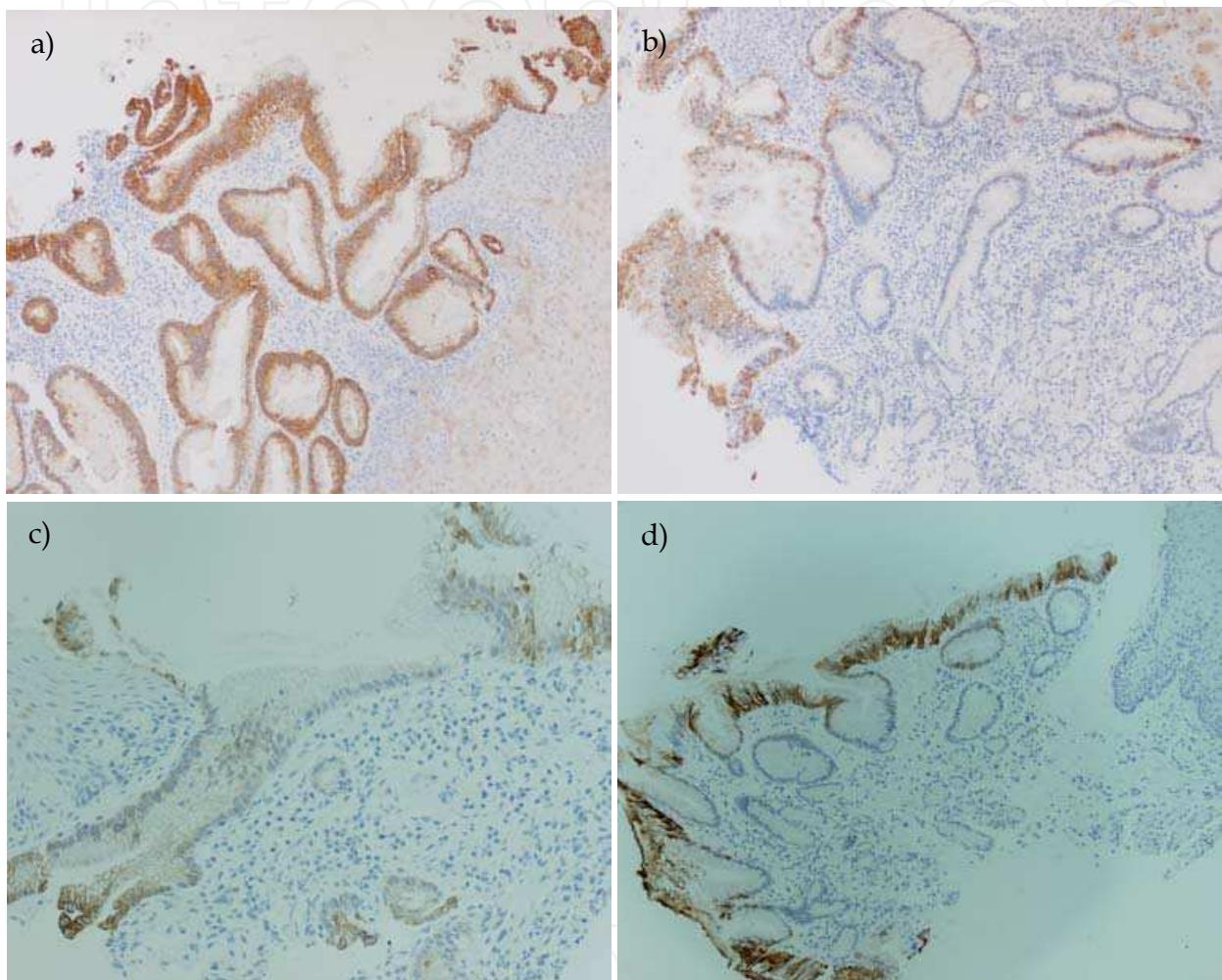


Fig. 5. (a) Cytokeratin (CK) 7 staining of HGMP/CIP showing uptake in the surface glandular tissue similar to that seen in Barrett's esophagus (b). CK20 staining uptakes are similar in HGMP/CIP (c) and Barrett's esophagus (d)

The HGMP/CIP can also be colonized by *Helicobacter pylori* and the patches are subjected to changes that are seen in the stomach (Akbayir et al., 2004; Alagozlu et al., 2010; Borhan-Manesh & Franum, 1991 & 1993; Gutierrez et al., 2003; Jacobs et al., 1997; Maconi et al., 2000; Poyrazoglu et al., 2009; Tang et al., 2004; Yüksel et al., 2008). Chronic inflammatory changes can be seen and progression to atrophy, intestinal metaplasia, dysplasia and malignant transformation have been reported (Borhan-Manesh & Franum, 1991). The surrounding squamous cell mucosa can also show inflammatory changes similar to those seen in reflux esophagitis (Borhan-Manesh & Franum, 1991).

4. Classification

A clinico-pathologic classification has been proposed by von Rahden *et al.* (von Rahden *et al.*, 2004) which categorized patients with HGMP into five groups (I to V) based on the clinical, endoscopic and histological findings (Table 1). This classification also takes into account of small patches that may be only visible microscopically. Based on this classification, majority of the HGMP/CIP are categorized into types I and II, asymptomatic and mildly symptomatic respectively. One study found that the most common lesions are types I (73%) and II (27%) lesions.

Category	Description	Symptoms/findings	Frequency
I	Asymptomatic	None	Common
II	Symptomatic	Laryngopharyngeal reflux	Common
III	Symptomatic with benign complications	Strictures/webs/fistula/bleeding * Polyps	Uncommon
IV	Intra-epithelial dysplasia	None/non-specific	Uncommon
V	Malignant transformation	Asymptomatic/dysphagia	Reported
<i>Suffix</i>			
a	inlet patch (macroscopically visible patch of HGMP/CIP)		
b	microscopic foci (only microscopically visible HGMP/CIP)		

Adapted from von. Rahden *et al.* Heterotopic gastric mucosa of the esophagus: literature-review and proposal of a clinicopathologic classification. *Am J Gastroenterol.* 2004; 99:543-51.

* Not included in the original classification

Table 1. Clinico-pathological classification for HGMP/CIP

5. Clinical manifestations

The majority of patients found to have HGMP/CIP are asymptomatic and the HGMP/CIP are usually detected incidentally while being evaluated with endoscopy for other gastrointestinal complaints. The clinical importance of HGMP/CIP remains controversial with some authors believe that they are benign and of no clinical relevance. Others have shown HGMP/CIP to be clinically important especially for a subset of patients with HGMP/CIP. For those who have symptoms attributable to the HGMP/CIP, most are mild and are detected only on direct inquiries. For a small proportion of patients, the symptoms can be prominent and patients may have many consultations before a diagnosis is made. The prevalence of any symptoms, typically those considered extra-esophageal symptoms complex of gastroesophageal reflux such as chronic cough, throat irritation or sore throat, regurgitation, globus pharyngeus, dysphagia or hoarseness ranges from very low to as high as 75% (Chong & Jalihal, 2010; Maconi *et al.*, 2000).

HGMP/CIP like other ectopic gastric mucosal have been proven to be able to secrete acid in sufficient quantity to induce inflammatory changes and acid related symptoms (Baudet *et al.*, 2006; Galan *et al.*, 1998; Hamilton *et al.*, 1986; Korkut *et al.*, 2010; Nakalima *et al.*, 1993; Yüksel *et al.*, 2008). Acid is the main cause of symptoms in patients with HGMP/CIP. Given the proximity of the HGMP/CIP to the laryngopharyngeal area, it is not surprising that

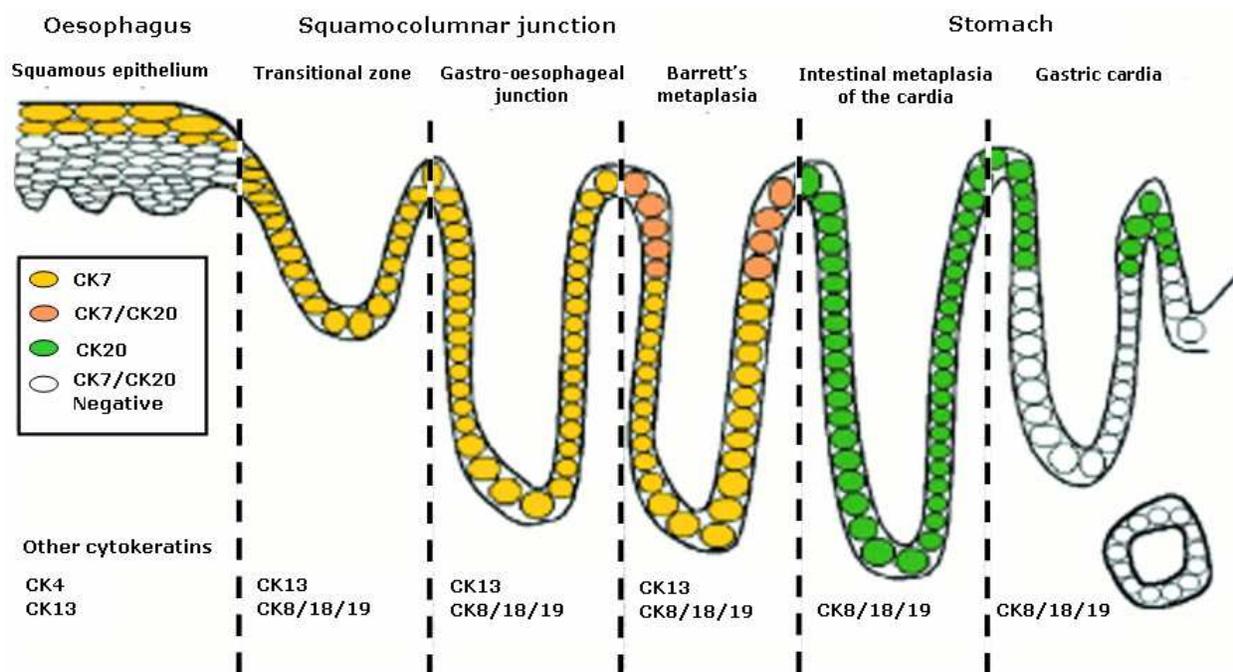


Fig. 6. Schematic illustration of cytokeratin (CK) 7 and 20 expression in the normal esophagus, Barrett's metaplasia, squamocolumnar junction, and proximal stomach. LATCHFORD A et al. *Gut* 2001; 49:746-747 (Reprinted with permission from *GUT BMJJournal*) (Latchford et al., 2001).

even weakly acidic secretion can cause symptoms. Others have proposed that mucin secretion can also cause symptoms (Bajbouj et al., 2009). Proximal esophagus dysmotility has also been shown to be associated with HGMP/CIP (Korkut et al., 2010).

Studies that had looked at specific groups of patients, such as those with laryngopharyngeal complaints, have found mixed results. The overall prevalence of HGMP/CIP was in the similar range compared to studies that had been carried out on patients coming for routine endoscopy. One study that had looked specifically at patients with laryngopharyngeal reflux found significantly more HGMP/CIP in patients than controls, those without LPR symptoms (11.4% vs. 1.6%, $p < 0.05$). These patients also had significantly more laryngeal acid reflux documented on pH study (Akbayir N. et al., 2004). Similarly, other studies have found more laryngopharyngeal reflux symptoms in patients with HGMP/CIP (Akbayir et al, 2004; Baudet et al., 2006; Borhan-Manesh & Franum, 1993; Tang et al., 2004). Another study looking at patients who had undergone funduplications for gastroesophageal reflux with laryngeal reflux only found one patient (3.4%) to have HGMP/CIP (Salminen & Ovaska, 2009). This patient had a small HGMP/CIP and the authors concluded that HGMP/CIP does not have a significant role in laryngopharyngeal reflux in patients with gastroesophageal reflux disease.

Unfortunately, all these studies have not inquired on the same symptoms complex and hence make comparison difficult.

Interestingly, only one study had assessed the size of HGMP/CIP on clinical symptoms and did not find significant differences (Chong & Jalihal, 2010). This study categorized HGMP/CIP to small/moderate (<15mm) and large (>15mm). Only cough was significantly more (50% vs. 8.3%, $p = 0.022$) common in patients with larger patch. Interestingly, patients with smaller HGMP/CIP were found to have more globus and regurgitation. Several explanations were given for the lack of correlations between size of HGMP/CIP and

symptoms and these include; a) missed patches, b) the mucosal types of HGMP/CIP and c) the underlying degree of inflammatory changes that can affect acid output. Patients with predominant antral mucosal type HGMP/CIP may not have or minimal acid related symptoms. Patients with severe inflammatory changes approaching atrophy may have reduce acid output, hence minimal symptoms. Interestingly, more patients with HGMP/CIP also experienced heartburn compared to those with HGMP/CIP. This patients either had non erosive gastroesophageal reflux or symptoms induced by acid secreted by the patch flowing down. One study showed that greater acid production was found in those with larger HGMP/CIP patch (Baudet et al., 2006).

6. Diagnosis

6.1 Endoscopic features

On endoscopy, HGMP/CIP appears as salmon or velvety colored patch that is clearly distinct to the slatey white esophageal squamous cell mucosa (Figure 7). A majority of HGMP/CIP is round or ovoid. Some can be elongated with the maximal dimension in the longitudinal direction. Rarely, HGMP/CIP can be so big that they cover almost or the entire circumference of the esophagus. Smaller patches tend to be round or oval, are usually elevated or flat with smooth texture and white edges. Larger patches tend to be depressed on maximal insufflations during endoscopic examination and are ovoid or elongated with jagged edges and nodular surface textures. Occasionally, inflammatory changes similar to those observed in reflux esophagitis can be seen at the edges. Most are single patch and

Authors [Ref]	Symptoms	Prevalence
Jacob et al [1997]	Symptoms inquired Pharyngeal discomfort, Globus, burning sensation in throat, odynophagia & dysphagia to liquid/solid	Overall, 9.1% (p=ns)
Maconi et al [2000]	Symptoms Dysphagia, throat discomfort and heartburn	Overall, 5.5% (p=ns) Overall, 22.2% (milder symptoms included)
Akbayir et al [2004]	Upper esophageal and laryngopharyngeal symptoms Individual symptoms not defined	Overall, 45% vs. 21.5% (p=0.07)
Baudet et al [2006]	Dysphagia	21 vs. 4.0, p<0.001
Poyrazoglu et al [2007]	Symptoms (not defined) Dysphagia	Overall not defined 39.4% vs. 0% (p<0.05)
Chong & Jalihal [2010]	Symptoms Chronic cough Sore throat/hoarseness Globus Regurgitation Heartburn	Overall, 73.1% (p<0.05) 29.2 vs. 10.6% (p<0.01) 54.2 vs. 11.7% (p<0.01) 23.1 vs. 7.1% (p<0.01) 42.3 vs. 13.1% (p<0.01) 50.0 vs. 22.5% (p<0.01)

Table 2. Prevalence of symptoms reported to be associated with HGMP/CIP

in patients with multiple patches, they tend to be found in close proximity, above or below forming columns or on the opposite side (kissing patches). It is uncertain whether the size of HGMP/CIP may change with time. One study reported that the size of a HGMP/CIP decreased during subsequent endoscopy whilst on acid suppression treatment (Chong & Jalihal, 2006). Healing of surrounding inflammation may account for this observation. Associated findings include elevated whitish nodules that do not have the characteristic salmon colored mucosa. In elderly patients, venous bleed or hematoma can also be found. To date, the profiles of HGMP/CIP have not been properly studied. Interestingly, HGM can also be found in other parts of the esophagus, mid esophagus and above the gastroesophageal junction (Borhan-Manesh & Franum, 1991; Katsanos et al., 2010) (Figure 7e).

It is likely that the overall acid production from the HGMP/CIP is less than that seen in gastroesophageal reflux disease affecting the gastroesophageal junction. Acid related injuries can be seen in the patch and the surrounding esophageal squamous mucosa. Inflammatory macroscopic changes visible during endoscopy or microscopic changes only visible on histological examinations resembling those seen in reflux esophagitis have been described.

7. Modalities for detection of HGMP

7.1 High definition endoscopy

Use of high definition endoscopy will improve the clarity and definition and can differentiate HGMP/CIP from the squamous mucosa.

7.2 Narrow band imaging

Narrow band imaging (NBI) which utilizes different light wavelengths has been reported to improve the detection rate of HGMP/CIP (Hori et al., 2010; Ohara, 2010). NBI allows better visualization of the more superficial features of mucosa. In NBI, the HGMP/CIP appears a grayish pink patch surrounded by greenish hued squamous cell mucosa. Occasionally area where the thickness of squamous cell layer is less, it can also give the similar appearance but in this case, mucosal vessels, greenish in appearance, can still be seen coursing through the area. In HGMP/CIP, vessels are not seen.

7.3 Chromoendoscopy

HGMP/CIP can also be visualized with chromoendoscopy. Both Lugol's solution and methylene blue can be used to identify HGMP/CIP. Lugol's solution is iodine based and has affinity that has affinity for glycogen in non-keratinized squamous cell epithelium of the esophagus. HGMP/CIP will not stain and appear lighter shade compared to the surrounding esophagus. Methylene blue will stain HGMP/CIP blue in colour. However, this procedure requires the spraying of dye and to do this in the proximal esophagus may induce cough reflex causing discomfort to the patient (Dib & Ortiz, 2009).

7.4 Wired guided examination

Use of wire guided examination has also been reported to improve the yield. The endoscope is withdrawn into the mid-esophagus and a guide wire is threaded through into the esophagus. The endoscope is then slowly withdrawn while examining the proximal esophagus and crico-pharyngeal area (Bhasin et al., 2006).

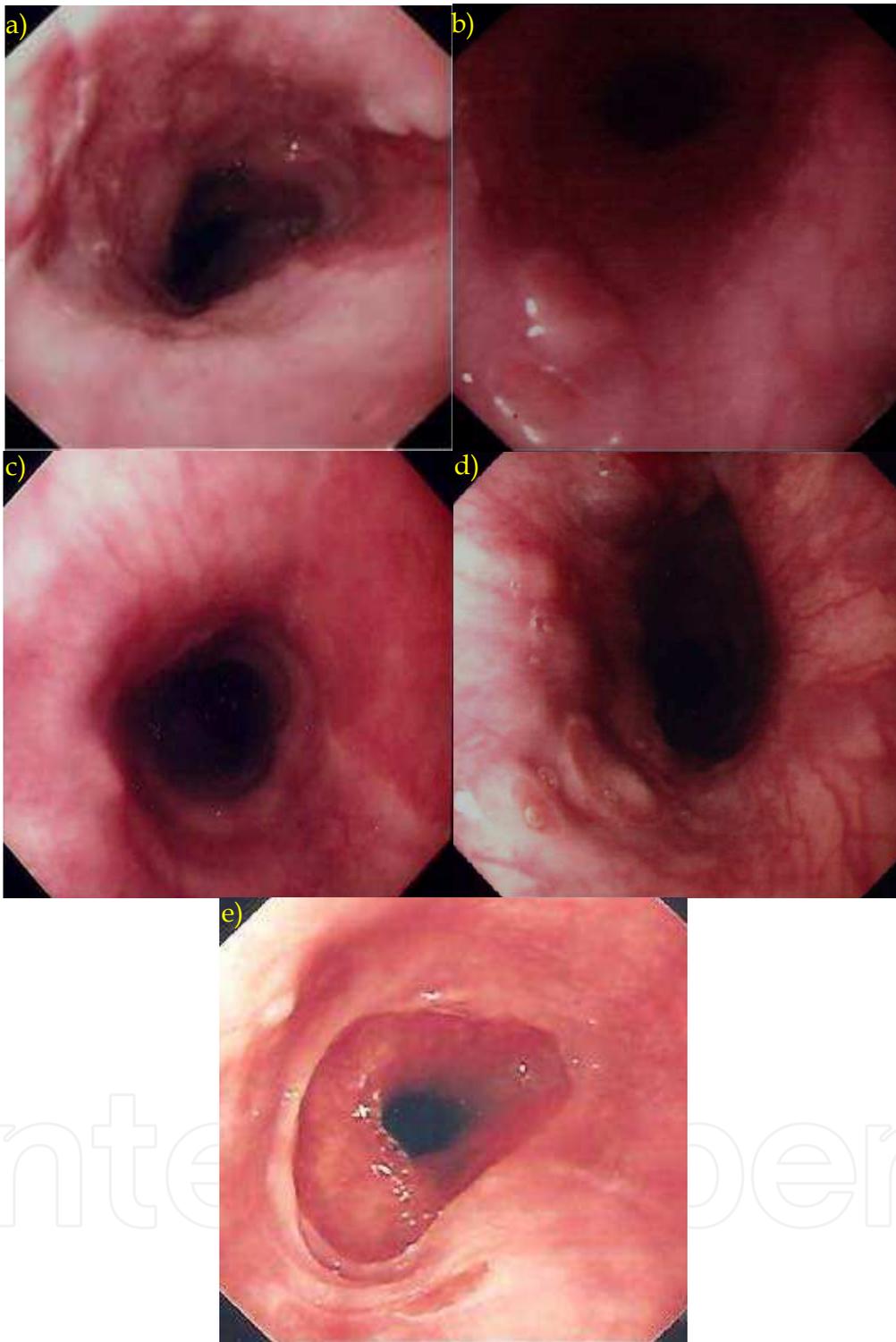


Fig. 7. Endoscopic images showing different HGMPs; a) a large depressed patch with coarse surface texture with another patch located on the opposite wall, b) two small patch with smooth surface texture, one elevated and the other flat, c) a large slightly depressed patch with coarse surface texture on the right lateral wall, d) two round elevated patch with white edges and smooth surface and associated venous bleed, and e) a small flat round patch with smooth surface texture located above the gastroesophageal junction. All the patches shown stained positive for CK7 and CK20 with characteristics pattern

7.5 Radio-nuclear imaging

Radio nuclear scan has been widely used for the detection of ectopic gastric mucosa especially in cases suspected to have Meckel's diverticulum (Kiratli et al., 2009). Technetium-99m pertechnetate scintigraphy can accurately localize the location of HGMP. The role and use of nuclear imaging in detecting HGMP/CIP remains unknown. One study reported its use in five patients with patches of gastric fundal type columnar epithelium in the proximal esophagus at the level of the upper esophageal sphincter diagnosed by upper endoscopy (Chen et al., 1989). In all instances, the patches contained both chief cells and mucus-secreting cells. Two cases of HGMP/CIP were demonstrated by TcO₄⁻. Unfortunately, TcO₄⁻ accumulation in the thyroid glands of three patients caused overlapping activity between the thyroid gland and HGMP/CIP. It was concluded that TcO₄⁻ scintigraphy is only suitable for patients who have had a total thyroidectomy or are on suppressive thyroid therapy.



Fig. 8. Narrow band imaging showing an ectopic gastric mucosal patch as salmon coloured patch with greenish background

7.6 Contrast fluoroscopy/Barium swallows

One study showed that careful fluoroscopy study can detect subtle abnormalities that may be due to HGMP/CIP (Takeji et al., 1995). This study detected 27 cases of HGMP/CIP confirmed on endoscopy and biopsy in 1,142 patients undergoing annual health check. The most common radiographic finding was a pair of small indentations on the wall of the esophagus (n=18). Other findings included a rim-like shadow (three patches), a pair of large indentations with a shallowly depression (two patches), one indentation (five patches), a small flat elevation (one patch), a serrated irregular outline (five radiologic lesions consisted of 11 patches), other various irregular outlines (two patches), and a polypoid area (one patch). One study using barium contrast swallow showed features similar to those described for esophageal webs and suggested that in fact, esophageal webs maybe due to HGMP/CIP (Ainley, 2011). This study clearly showed that HGMP/CIP produced the same imaging features of esophageal web on barium swallow. Chronic acid injuries lead to inflammations and subsequent healing results in a web or stricture formation. This has been referred to as type AA ring in contrast to the A (muscular ring) and B (Schatzki ring) rings in the distal esophagus.

7.7 Others

Use of proximal pH monitoring can also provide clue to the presence of HGMP/CIP. Presence of acid pH detected in the proximal esophagus without acidic pH detected in the distal esophagus suggests the presence of HGMP/CIP. However, both gastroesophageal reflux and proximal acid reflux secondary to HGMP/CIP may co exist. Endoscopic imaging will still be required to confirm the presence of HGMP/CIP. Use of confocal microendoscopy for the diagnosis has also been reported.

8. Complications

Complications of HGMP/CIP are those cases classified under the clinico-pathological classification as types III to V (von Rahden et al., 2004). To date, there have been around thirty cases of cervical esophagus adenocarcinoma (type V) reported (Abe et al., 2004 ; Alaani et al., 2007 ; Alrawi et al., 2005 ; Balon et al., 2003; Berkelhammer et al., 1997; Carrie, 1950; Chatelain et al., 2002; Christensen & Sternberg, 1987; Clemente, 1974; Danoff et al., 1978; Davis et al., 1969; Goëau-Brissonnière et al., 1985; Haruki et al., 2008 ; Hirayama et al., 2003; Ishii et al., 1991; Kammori et al., 1996; Kamiya et al., 1983; Klaase et al., 2001; Lauwers et al., 1998 ; Morson & Belcher, 1952; Noguchi et al., 2001 ; Pai et al., 1997; Pech et al., 2001; Raphael et al., 1966; Sakamoto et al., 1970; Schmidt et al., 1985; Sperling & Grendell, 1995; Takagi et al., 1995; von Rahden et al., 2004 & 2005; Yoshida et al., 1986; Yoshida et al., 2010) in the literature. Other non-malignant complications (types III and IV) have been reported in both children and adults and are shown in Table 1 (Sauvé et al., 2001; Mion et al., 1996; Steadman et al., 1988; Yarborough et al., 1993; Boshier & Taylor, 1951; Powell & Luck, 1988; Karnak et al., 1999; Buse et al., 1993; Waring & Wo, 1997; Weaver, 1979; Bataller et al., 1995; Kohler et al., 1988; Garcia et al., 2002; Daher et al., 2010; Sánchez-Pernaute et al., 1999; Righini et al., 2007 ; Chatelain et al., 1998; Oguma et al., 2005 ; Rana et al., 2006 ; Schulewitz et al., 2007). Proximal esophageal web or stricture associated with Plummer-Vinson or Paterson-Kelly-Brown syndrome associated with sideroblastic anemia is now believed to complication of HGMP/CIP (Ainsley, 2011). Table 3 shows the listed of reported complications associated with HGMP/CIP.

8.1 Other possible associated with HGMP/CIP

Other conditions reported to be associated with laryngopharyngeal reflux include chronic obstructive airway disease exacerbations, obstructive sleep apnea and laryngopharyngeal neoplasms (Eryuksel et al., 2009; Wise et al., 2006; Copper et al., 2000). Indirectly, there may be association with HGMP/CIP (Basseri et al., 2009; Satoh et al., 2007).

9. Treatment/management

The management of patients with HGMP/CIP depends on the presence of symptoms or complications following the clinico-pathological classification proposed by von-Rahden. For the majority of patients, HGMP/CIP are detected incidentally (type I) and as such do not require any treatment, follow up or surveillance. For patients with acid related symptoms, treatment with acid suppression with or without pro-kinetic and antacid will suffice. For majority, a short course of treatment will be adequate. However, for a proportion, prolonged acid suppression similar to patients with significant gastro-esophageal reflux disorders may be required.

Other reported modalities for treating symptomatic non neoplastic HGMP/CIP include argon plasma coagulation and endoscopic mucosal resection. However, these modalities have only been reported in small series.

For those cases with complicated HGMP/CIP (type III), apart from acid suppressions, other modalities such as dilatation for stricture and even surgery may be required.

Type IV cases will require close follow up treatment may include argon plasma coagulation (Sauvé et al., 2001; Klaase et al., 2001), endoscopic mucosal resection (EMR) and endoscopic sub-mucosal dissection (ESD). For those with type V HGMP/CIP, treatment will depend on the stages of disease. Early adenocarcinoma can be treated with EMR or ESD. These can be resected after the creation of a polyp by rubber band ligation or with cap assisted EMR. For other cases, surgical resections are indicated.

It remains unknown whether patients detected to have HGMP/CIP requires to be followed up for future complications or progressions to types III to V. Patients found on biopsy to have dysplastic HGMP/CIP mucosa will require surveillance. It is unknown what time interval is recommended. Given that HGMP/CIP is gastric mucosa, following the recommendations for stomach will probably be adequate.

10. Controversies

Currently, there are several controversies regarding HGMP/CIP. First, there is still dispute with regard to the origin of HGMP/CIP. However, it is widely believed to be congenital origin as result of remnant of columnar epithelium due to failure of complete squamization of the esophagus. There are several factors that favor the congenital origin hypothesis. The embryogenesis of esophagus can explain the profiles of HGMP/CIP; proximal location correlating with the last part of the esophagus, the proximal esophagus to transform to keratinized mucosa. Babies and children do not have sufficient duration of acid exposure to induce changes suggested by the acquired theory. Finally, although the staining pattern based on CK7 and CK20 are similar, staining with MUC protein shows differences between HGMP/CIP and Barrett's (Lauwers et al., 2005).

An earlier study had also shown that the HGMP/CIP had cellular component different from Barrett's esophagus, suggesting embryogenic in origin (Fuerle et al., 1990).

The proposed theory on acquired origin was based on similarities between histological findings of HGMP/CIP and Barrett's esophagus. Mucin protein (MUC) and CK7 and CK20 similarities suggested similar origin. Other study based on MUC also suggested HGMP/CIP being acquired in origin. In the future, other staining methods may be identified and may show clear differences between HGMP/CIP and Barrett's esophagus. Weak evidence come from higher incidence of Barrett's esophagus in patients found to have HGMP/CIP. However, the overall reported incidence rates are still too low to lend strong support for this theory.

The latest theory proposed was based on findings of glandular cystic retentions secondary in the proximal esophagus. The evidence to support this theory are lacking given the very few reports of glandular retention cysts encountered in the clinical practice and reported in the literature. Furthermore, the absence of lesions found in the other part of esophagus makes the second and the third proposed theories less likely. Interestingly, it has also been proposed that the origin may be different, congenital in baby or children and acquired in adult (Lauwers et al., 2005).

Second, the actual incidence of HGMP/CIP is not exactly known. Earlier endoscopic studies have reported rates ranging from 0.35 to 10.0% and a latest study that had used NBI reported a rate of 13.8% (Ohara, 2010). An autopsy studies have reported rate as high as 70%. However, autopsy studies on paediatric population in the mid-twentieth century had only reported rates of less than 10%. With the advent of newer imaging modalities that provide superior endoscopic images, this will provide more accurate incidence. The true incidence rates are likely to be close to the rates reported by NBI studies given the clear distinction of HGMP/CIP observed with NBI. In future studies, it is very important that the endoscopists are aware and to look for this lesions. Several studies have already reported that the pick up rates were higher when endoscopist were aware of the entity (Maconi et al., 2000; Azar et al., 2007).

The third controversy relates the clinical significance of HGMP/CIP in clinical practice. While many have found low prevalence of symptoms in associated with HGMP/CIP, it is no doubt that HGMP/CIP have clinical significance given the reported complications that include malignant transformations.

Other controversies include suggested association with extra-esophageal cancers in the aero-digestive tract. Incidence of laryngeal carcinoma has been shown to be higher in patients with laryngopharyngeal reflux disorder (Copper MP et al., 2000).

11. Future areas

HGMP/CIP remains a mysterious entity that have not been well studied compared to other esophageal disorders. Encouragingly, in the last decade, the number of publications on HGMP/CIP has been increasing. However most of these studies have only looked at the clinical and histological profiles without further addressing newer areas that can help to address the controversies that still surround HGMP/CIP. Future areas of interest include addressing the controversies that still surround HGMP/CIP. Other areas of interest are highlighted in Table 4.

12. Overview

Endoscopy is important part of our armamentarium for the evaluation of suspected gastrointestinal pathologies. Significant pathologies commonly encountered in the upper gastrointestinal tract include gastro-esophageal reflux related disorders (esophagitis, ulcers and strictures), varices, esophageal tumor, gastric ulcers, gastric tumor and duodenal ulcers. Most clinicians and endoscopists are aware of these pathologies. The proximal esophagus is frequently neglected during endoscopy with little time spent to examine this area. Pathologies found in or around the proximal esophagus include HGMP/CIP, Zenker's diverticulum, esophageal web, downhill varices and venous blebs or hematoma.

HGMP/CIP is an interesting clinical entity that still hold many mysteries and is still relatively under-recognized and unknown to many clinicians, even those who manage patients with laryngopharyngeal reflux disorders. It was first reported by Schmidt in 1805 (Schidmt, 1805). There are still very few publications compared to other esophageal disorders and only in the last decade the number of publications on this entity has increased, albeit slightly.

The proximal location of the HGMP/CIP contributes to the low detection as this area is difficult to examine. Endoscopists need to be aware and look for this condition. Studies have

shown higher pick up rate when the lesions are being looked for. HGMP/CIP can also be found in the other part of the esophagus. On endoscopy, HGMP/CIP appears as a salmon-colored or velvety patch on white light endoscopy that is distinct from the esophageal squamous mucosa. HGMP/CIP may appear different color on other imaging techniques. Use of confocal endoscopy has been reported for the diagnosis of HGMP/CIP (López-Cerón Pinilla M et al., 2011). Majority of HGMP/CIP are solitary but can be multiple and the sizes can range from very small to very large. In patients with multiple patches, they are usually small and are located in close proximity of each other. They are typically found on the right or left lateral esophageal wall but can also be circumferential. They are usually oval, ovoid or round but can be elongated in shape.

Current controversies

- Origin of HGMP/CIP- Congenital/ Acquired
- Clinical significance
- Exact incidence

Others

- Best method of detection
 - Magnification endoscopy
 - Narrow band imaging
 - Chromoendoscopy
 - Others
- Role of measuring acid output and clinical correlation with symptoms
- Method of measuring the surface area- Exact size of HGMP/CIP
- Role in clinical symptoms
 - Acid
 - Non acidic secretion
- Surrogate markers of histological activities of HGMP/CIP
- Treatment modalities for the various types of HGMP/CIP
- Role of Helicobacter pylori in histological progression and malignant transformation

Table 4. Future areas to address on HGMP/CIP

HGMP/CIP is reported to cause laryngopharyngeal reflux or extra-esophageal symptoms of gastro-esophageal reflux disorder. The reported frequency of laryngopharyngeal reflux symptoms ranged from very low to as high as 75% in patients with HGMP/CIP (Chong & Jalihal, 2010). Fortunately, most laryngopharyngeal reflux symptoms are mild. However, complications such as ulcerations, strictures, perforation and malignant transformation have been reported (von Rahden et al., 2004). Associations with higher frequency of laryngopharyngeal malignancies in patients with laryngopharyngeal reflux have also been reported.

The current clinico-pathological classification proposed by von-Rahden *et al.* provides a useful classification of the various manifestations of HGMP/CIP (von Rahden et al., 2004). It also guides clinical management which largely depends on the presence and severity of symptoms. Management is mainly with pharmacotherapy and instrumentations (endoscopic) and surgery may be required for complicated cases. Ablative therapies with argon plasma coagulation have been reported to provide symptoms relieve or cure in those with globus

pharyngeus (Bajbouj M et al., 2009). Use of argon plasma has also been reported to be effective for dysplasia and early carcinoma. EMR or ESD have been reported to be successful for curative treatment of pT1 lesions whereas surgery is required for more advanced lesions. Controversies remain regarding the origin, clinical significance and the true incidence of HGMP/CIP. From current available evidence, it seems more likely that HGMP/CIP is congenital in origin. Despite the overall benign nature of the condition with most being categorized as type I (asymptomatic), serious complications including malignant transformation have been reported. It remains unknown how malignant transformation occur; whether it follows the established sequence of atrophy, metaplasia, dysplasia to neoplasia for Barrett's adenocarcinoma or *Helicobacter pylori* associated adenocarcinoma sequence.

Interesting future areas include studies to address the controversies mentioned, the role of newer imaging techniques to increase the diagnosis and distinguish the underlying histological profiles of HGMP/CIP, the role and significance *Helicobacter pylori* in symptoms or histological progression (whether it share similarities with gastric and *Helicobacter pylori*), ways of measuring size of patch and acid output, role of acid or mucin secretion in symptoms and possible surrogate markers for assessing histological activities of the HGMP/CIP. Biopsies of the HGMP/CIP can be difficult and it is uncertain whether the histological activities of HGMP/CIP parallel that of the gastric mucosa within the antrum, body or fundus.

13. References

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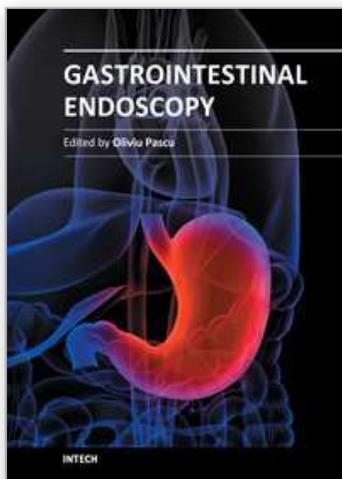
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Endoscopy has had a major impact in the development of modern gastroenterology. By using different data it provided a better understanding of pathogenic mechanisms, described new entities and changed diagnostic and therapeutic strategies. Meanwhile, taking advantage of many technical advances, endoscopy has had a developed spectacularly. Video-endoscopes, magnification, confocal and narrow-band imaging endoscopes, endoscopic ultrasounds and enteroscopes emerged. Moreover, endoscopy has surpassed its function as an examination tool and it became a rapid and efficient therapeutic tool of low invasiveness. InTech Open Access Publisher selected several known names from all continents and countries with different levels of development. Multiple specific points of view, with respect to different origins of the authors were presented together with various topics regarding diagnostic or therapeutic endoscopy. This book represents a valuable tool for formation and continuous medical education in endoscopy considering the performances or technical possibilities in different parts of the world.

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