

CLINICAL REVIEWS

Heterotopic Gastric Mucosa of the Esophagus: Literature-Review and Proposal of a Clinicopathologic Classification

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The prevalence of heterotopic gastric mucosa (HGM) in the cervical esophagus is frequently underestimated. Tiny microscopic foci have to be distinguished from a macroscopically visible patch, also called "inlet patch." Symptoms as well as morphologic changes associated with HGM are regarded as a result of the damaging effect of acid, produced by parietal cells in the mostly fundic type of HGM.

We herein review the literature and propose a new clinicopathologic classification of esophageal HGM: Most of the carriers of esophageal HGM are asymptomatic (*HGM I*). Some individuals with HGM in the esophagus complain of dysphagia, odynophagia, or "extraesophageal manifestations" (hoarseness and coughing), without further morphologic findings (*HGM II*). Still fewer patients are symptomatic due to morphologic changes, *i.e.*, esophageal strictures, webs, or esophagotracheal fistula (*HGM III*). Malignant transformation via dysplasia (intraepithelial neoplasia, *HGM IV*) to cervical esophageal adenocarcinoma (*HGM V*) is exceedingly rare (only 24 reported cases). In contrast to Barrett's esophagus, HGM should not be regarded as a precancerous lesion.

Symptoms are more likely to occur in patients with inlet patch, whereas malignant transformation and adenocarcinogenesis can also occur in microscopic HGM foci. Asymptomatic HGM requires neither specific therapy nor endoscopic surveillance. Only in symptomatic cases treatment, *i.e.*, dilatation for (benign) strictures or acid suppression for reflux symptoms, can be recommended. Patients with low-grade dysplasia in HGM might be candidates for surveillance strategies, whereas in cases of high-grade dysplasia and invasive adenocarcinoma oncological treatment strategies must be employed.

INTRODUCTION

Heterotopic gastric mucosa (HGM) is frequent in the cervical esophagus, but most carriers are asymptomatic. Nevertheless it can be responsible for local morphologic alterations (*e.g.*, webs, strictures, ulcers, fistula) causing local symptoms (especially pain and dysphagia). Furthermore, in exceedingly rare cases, HGM can be the origin of malignant progression to cervical esophageal adenocarcinoma.

HGM is not exclusively found in the esophagus as it has also been described in other localizations throughout the gastrointestinal tract, like the tongue (1), the duodenum (2), the jejunum (3), the gall bladder (4), and the rectum (5).

The extent of HGM can vary from tiny microscopic foci to macroscopically visible areas of red or salmon-colored velvety patches. Predominant localization of esophageal HGM is the region immediately below the upper esophageal sphincter. Such patches of macroscopically visible HGM are also called "inlet patches."

Although the first description of a gastric inlet patch in the esophagus dates back 200 yr when Schmidt in 1805 was the first to describe this entity (6), many questions concerning etiology, pathophysiology, and treatment remain unanswered.

METHODS

Selection of articles for this review was based on a computerized MEDLINE database search for relevant literature, using the search terms "ectopic gastric mucosa," "heterotopic gastric mucosa," "gastric inlet patch," and "gastric heterotopia." Articles were checked and included if relevant new information on the topic were provided. The literature search encompassed the years available online. Additionally, prior articles cited in the papers were included if relevant.

Epidemiology

Epidemiologic data concerning HGM are scarce. The exact prevalence, the frequency of symptomatic cases, and the

incidence of malignant progression to cancer are vaguely known.

Historical investigations revealed a prevalence of 0.67% (7) to 70% when microscopically visible foci were included (8). The largest autopsy series (1,000 autopsies in children) by Rector and Connerly revealed aberrant gastric mucosa in the upper esophagus in 4.5% of the cases (9). Unfortunately this interesting question has not been addressed in more recent studies.

In endoscopic studies, HGM patches are found in 0.1–10% of the cases (10–14), but the frequency tends to be clinically underestimated.

The latter is due to the predominant localization in the region immediately below the upper esophageal sphincter: This area is not easily accessible by endoscopy as it is just below the scope of the otolaryngologist and exploration by flexible upper gastrointestinal endoscopy is difficult: The region is quickly passed protruding the endoscope over the sphincter's resistance and only by gently withdrawing the instrument can an inlet patch be detected (12, 13).

Pathology

The size of esophageal “inlet patches” (Fig. 1) varies from 0.2 to 0.3 cm to 3 × 4 cm (12). They can be unique or multiple, round or oval, can extend transversally or circumferentially. The surface can be flat, slightly raised, or depressed, sometimes with heaped margins (15) (see Figs. 1 and 2)

The histologic appearance of HGM is fairly characteristic (see Figs. 3 and 4) although esophageal mucosal glands can be mistaken for HGM (16). Mostly the gastric mucosa is uniformly of the fundic-type, containing parietal cells (10, 12). Less frequently, histopathologic examination of HGM shows a “transitional” cell type with random admixture of fundic and antral glands or an “antral” pattern, defined

by the absence of chief cells and only few parietal cells (10). Sometimes these types are mixed (15). Chronic inflammation (infiltration of inflammatory cells) may be present and varies in extent (10, 15). Infiltration with granulocytes as well as lymphocytes and plasma cells can be observed (10, 15). Very common is the coexistence of esophagitis in the squamous mucosa adjacent to the HGM (12).

Inherited Condition or Metaplastic Change?

Esophageal HGM is generally regarded as a congenital condition, resulting from an incomplete embryologic esophageal epithelization process: The columnar epithelium of the embryo's esophagus is gradually replaced by squamous cell epithelium. This process starts in the midesophagus and extents vertically in both directions with the cervical esophagus being the last region to get stratified (17, 9, 18). If the squamous epithelization remains incomplete, the persisting columnar-lined area differentiates to HGM.

The development of the esophageal lumen and the pattern of epithelization is illustrated in Figure 5. Cell types (columnar/squamous cells), cell layers and special features of the cells (vacuoles/cilia/glands), and the size of the esophageal lumen at the certain stages of mucosal development are illustrated. The features are correlated with the length of the embryo.

Barrett's esophagus has formerly also been regarded as a congenital condition, but nowadays it is generally accepted that it is an acquired metaplastic change due to chronic gastroesophageal reflux. Repeatedly attempts have been undertaken to find an association between Barrett's esophagus and HGM (19, 14). Avidan *et al.* judged from their findings in a large case control study (53 patients with inlet patch and 4,882 control subjects) that the coincidence of the cervical

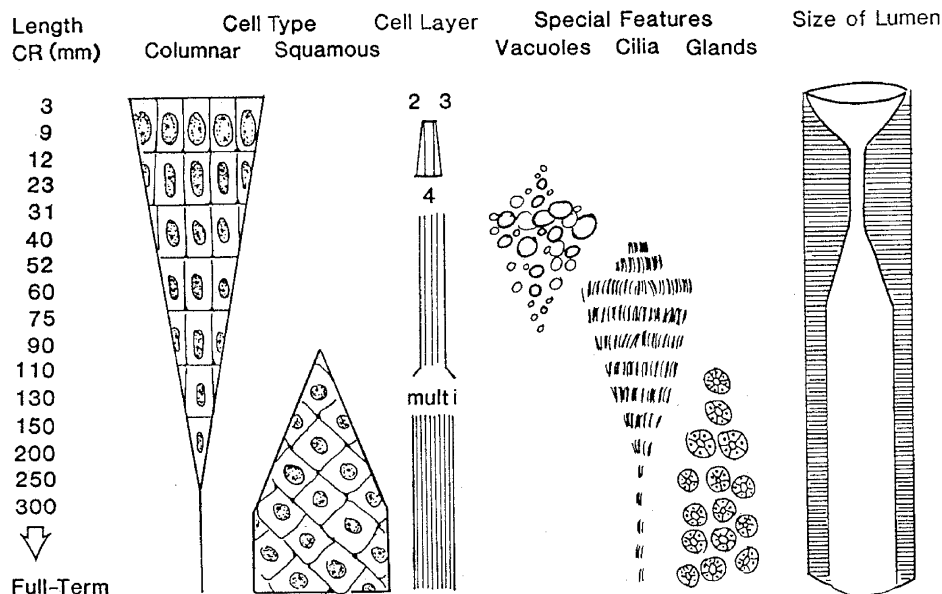


Figure 1. Development of the Mucosa in the human esophagus (from (17)).

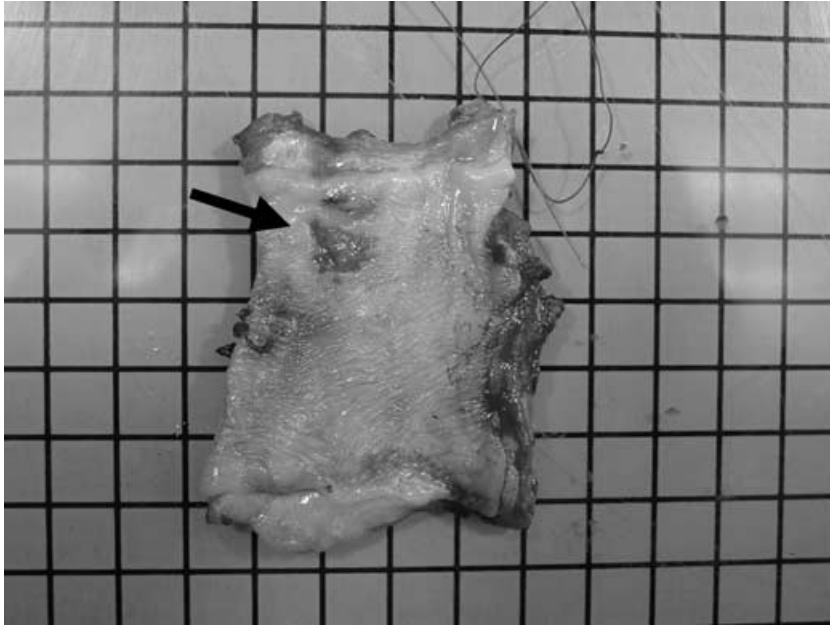


Figure 2. Grossly visible HGM just below the upper esophageal sphincter (inlet patch). The red-colored velvety patch was incidentally found after limited resection of the cervical esophagus succeeding neoadjuvant radiochemotherapy of an esophageal squamous cell cancer with complete response.

inlet patch and Barrett's esophagus could suggest a shared embryonic etiology (14).

Malhi-Chowla *et al.* reported, that in patients treated for high-grade dysplasia in Barrett's epithelium, the prevalence of HGM in the cervical esophagus is much higher and accounts for one-third of these patients (19). The authors concluded that patients with HGM might be at higher risk for

developing high-grade dysplasia in Barrett's esophagus and thus HGM might be a suitable marker.

Furthermore it has been suggested that HGM shares pathophysiologic and morphologic characteristics with Barrett's esophagus: Areas of intestinal metaplasia have been reported to occur within ectopic gastric mucosa (20, 15). Similarities of the mucin profile of HGM and Barrett were

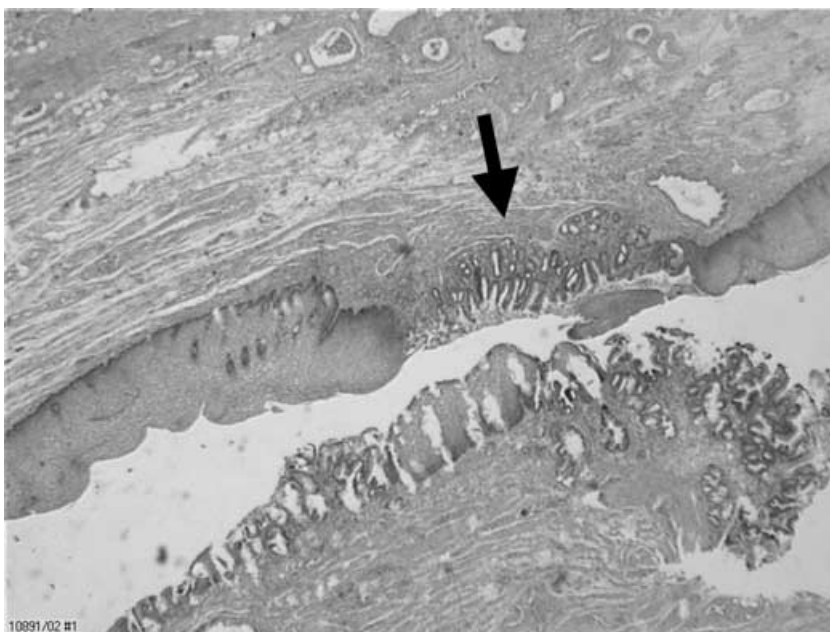


Figure 3. Microscopic examination shows the glandular differentiated tissue, interposed between normal esophageal squamous cell epithelium (H.E., 12x).

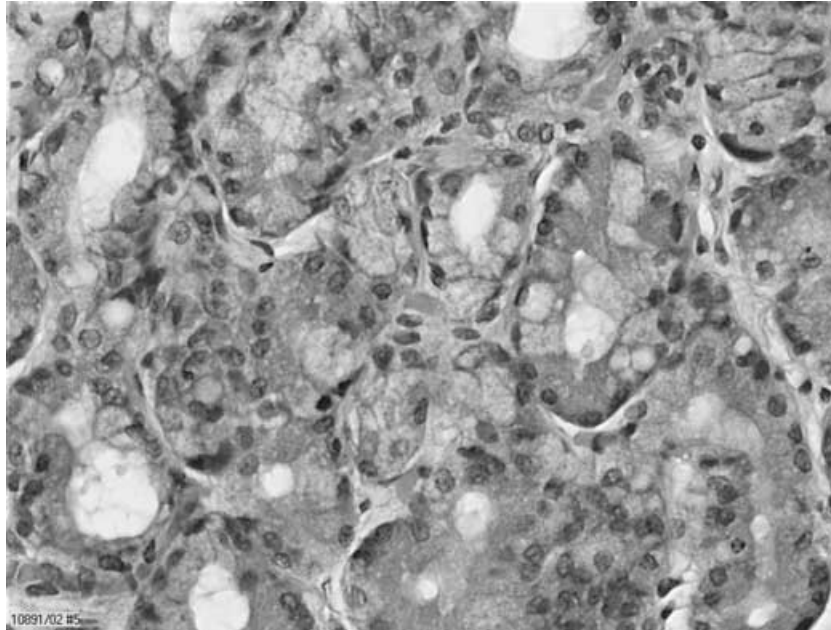


Figure 4. HGM consisting of well-differentiated gastric tissue with mucus-secreting columnar cells, chief cells, and parietal cells (H.E., 200x).

regarded as suggestive of a pathogenic link between these entities (16).

Since it has been suggested by Ormsby *et al.* that Barrett's esophagus can reliably be distinguished from intestinal metaplasia of the stomach according to a specific cytokeratin staining pattern (21), much interest has been focused on the immunohistochemical characterization of esophageal glandular epithelia. Although different authors have thus far supported the findings by Ormsby, the diagnostic significance of the CK7 positive/CK20 negative phenotype is not generally accepted (*e.g.*, (22)). Recently Chatelain *et al.* have

demonstrated the presumably Barrett-specific CK7+/CK20– staining pattern in HGM of a patient with associated cervical esophageal adenocarcinoma (23). The authors concluded from these findings (in addition to the considerations that HGM shares “some common clinical features with Barrett's esophagus”) that both—Barrett and HGM—have a common pathogenesis, related to gastroesophageal reflux disease.

Others hypothesized that some features reminding of Barrett's esophagus when examining HGM are suggestive for a superimposed acquired component to an underlying congenital lesion (16).

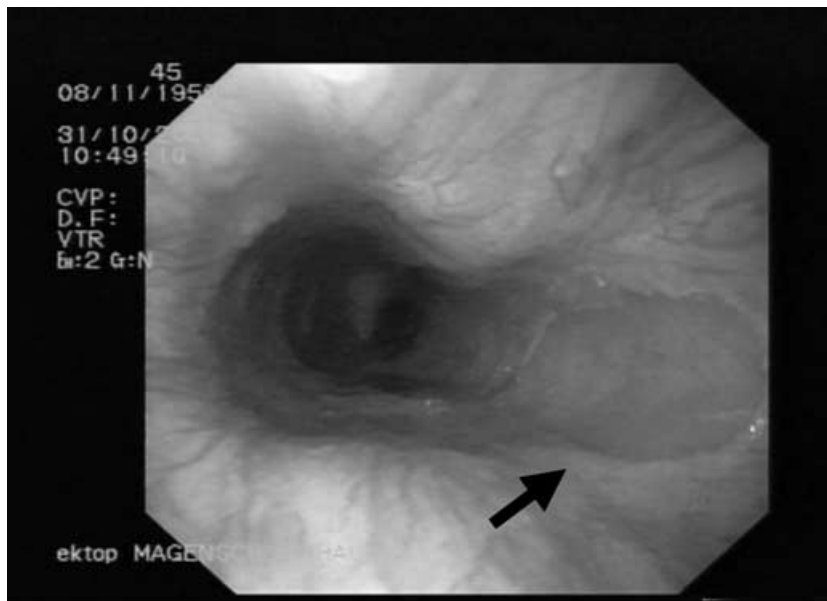


Figure 5. Fiberoptic endoscopic view of a large inlet patch, size 2.5 × 1 cm, localized immediately below the upper esophageal sphincter.

Despite all controversy, the origin of esophageal HGM has not been finally determined as yet, and further investigations are needed to resolve these questions.

Pathophysiology: Acid is the Evil Agent

Acid is the damaging agent in the pathophysiology of *symptomatic* esophageal HGM. Gastric parietal cells of the ectopic gastric tissue have been proven to be able to secrete a pathophysiologically effective amount of acid (10, 24–26). This acid can induce chronic inflammation and ulceration. The subsequent healing process can lead to formation of esophageal strictures and webs (24, 27–29).

Acid production has been demonstrated by congo red staining after stimulation with pentagastrin (25). The secretion has also been demonstrated using a pH electrode attached to a standard fiberoscope (26) or by continuous ambulatory pH monitoring (24).

It has been shown that the pH in the area of the inlet patch is less than 4, but the pH milieu in the distal esophagus is not affected. This is because the relatively small volume secreted is neutralized by saliva (24). Furthermore a meal-related secretion pattern (at daytime in the upright position) rather than a histamine-induced secretion pattern (at night time) has been revealed by the study.

It has been assumed that in view of the functional capacity of the HGM patches to produce acid, larger patches are more likely to produce symptoms (12).

Symptoms (dysphagia) as well as presumable “extraesophageal” manifestations of the acid production (coughing, hoarseness) are resolved by acid suppression therapy with a proton pump inhibitor (24).

In the literature cervical dysphagia due to upper esophageal rings and webs associated with iron-deficiency anemia has been subsumed under *Paterson–Kelly* or *Plummer–Vinson syndrome* or termed *sideropenic dysphagia* (30–32). Later, HGM has been suggested as a possible cause of this syndrome (28, 33): Functionally active (acid secreting) HGM causes peptic lesions in the cervical esophagus, which may heal through a reparative process with formation of ring-like membranes/webs. The facultative sign of iron-deficiency anemia can result from chronic blood loss due to erosive lesions.

The clinical importance of HGM is limited to symptomatic cases. Symptoms, signs, and complications are acid-related. Predominant symptoms are dysphagia (34) and pain/odynophagia. These result from different pathologic changes, like formation of stenosis/strictures or webs (for review see Ward *et al.* (29, 35, 26, 27)), esophageal spasms and esophagotracheal fistula (36), and colonization/infection with *Helicobacter pylori* (37, 38).

Malignant progression to adenocarcinoma is exceedingly rare, with only 24 cases reported in the world literature to date (the literature on published cases is listed in Table 1). Macroscopic suspicion of malignant transformation requires histological confirmation by means of biopsy. The specimen should be collected—as in most suspect lesions—from the center of the area. But reaching the lesion with the biopsy for-

ceps is sometimes technically difficult, due to the localization immediately below the sphincter (33).

Histologic confirmation of malignant behavior can appear difficult as well: Sperling and Grendell (39) as well as Carrie (40) reported about adenocarcinomas proven only during subsequent surgical resection.

The association between *H. pylori* and pathogenesis of active chronic gastritis and duodenal as well as gastric ulcers has been well described (41). A strong affinity of this microorganism to colonize gastric type mucosa has been demonstrated. By contrast HGM has been shown to be only colonized with *H. pylori*, when the bacterium is also present in the stomach (37, 38). Colonization of HGM was not observed in absence of HP in the stomach. Furthermore in this study there was no apparent correlation between positivity of HP and acute or chronic inflammation in HGM patches. Thus it is unlikely that peptic ulcer complications in HGM are dependent on HP colonization, although this question has not been answered in this study.

Another recent endoscopic biopsy study on *H. pylori* colonization of inlet patches (38) confirmed these results and found a prevalence of 73% (in 27 of 37 patients with *H. pylori* gastritis and HGM in the esophagus the inlet patch was also colonized). Interesting hypotheses have been proposed that HGM colonized with *H. pylori* might be a potential reservoir for oral–oral transmission or a niche where antibiotics might have difficulty reaching (38).

Malignant Transformation and Adenocarcinoma in the Cervical Esophagus

The low frequency of malignant transformation of HGM in the cervical esophagus as compared to Barrett’s esophagus in the distal esophagus suggests that it may not be regarded as a premalignant lesion. Malignant progression of HGM is—compared to its high prevalence—an exceedingly rare and sporadic event, which is much less frequent than malignant transformation of other tissues more commonly involved in carcinogenesis, *e.g.*, colonic mucosa.

Presumably, malignant progression within HGM occurs in a stepwise pattern—similar to malignant changes in other epithelia: The heterotopic, but otherwise “normal” epithelium initially may change to low- and then high-grade dysplasia (“intraepithelial neoplasia” according to the new nomenclature recently introduced by the WHO (42)) and finally advance to invasive carcinoma: This might be similar to malignant transformation of Barrett’s esophagus, following a metaplasia-dysplasia-carcinoma-sequence and for colorectal cancer, for which an adenoma-carcinoma sequence has been well described (43). However, so far only exceedingly few cases of high-grade dysplasia in esophageal HGM have been reported (44–46).

New Clinicopathologic Classification

We propose a new clinicopathologic classification of esophageal HGM that summarizes current knowledge about

Table 1. Published Reports on Cervical Esophageal Adenocarcinoma Arising in Heterotopic Gastric Mucosa (in chronological order)

Cases	Authors	Year	Title
1	Carrie (40)	1950	Adenocarcinoma of the upper end of the esophagus arising from ectopic gastric epithelium
2	Morson and Belcher (51)	1952	Adenocarcinoma of the esophagus and ectopic gastric mucosa
3	Raphael et al. (52)	1966	Primary adenocarcinoma of the esophagus: 18-year review and review of the literature
4	Davis et al. (53)	1969	Polypoid adenocarcinoma of the cervical esophagus
5	Sakamoto et al. (54)	1970	Primary adenocarcinoma arising from heterotopic gastric glands of the esophagus
6	Clemente (55)	1974	[A case of adenocarcinoma of the upper third of the esophagus arising on ectopic gastric tissue (author's transl)]
7	Danhoff (56)	1978	Primary adenocarcinoma of the upper esophagus
8	Kamiya et al. (57)	1983	[A case of primary adenocarcinoma of the cervical esophagus arising from ectopic gastric mucosa]
9	Goeau-Brissonniere et al. (58)	1985	[Adenocarcinoma of the cervical esophagus. Association with a gastric heterotopia]
10	Schmidt et al. (59)	1985	[Adenocarcinoma of heterotopic gastric mucosa in the proximal esophagus]
11	Yoshida et al. (60)	1986	Early detection of adenocarcinoma of the esophagus—Series of 52 primary esophageal adenocarcinomas, one arising in heterotopic gastric mucosa
12 + 13	Christensen and Sternberg (20)	1987	Adenocarcinoma of the upper esophagus arising in ectopic gastric mucosa — Two case reports and review of the literature
14	Ishii et al. (61)	1991	Case report: Adenocarcinoma of the cervical oesophagus arising from ectopic gastric mucosa
15	Sperling & Grendell (39)	1995	Adenocarcinoma arising in an inlet patch of the esophagus
16	Takagi et al. (62)	1995	Early adenocarcinoma arising from ectopic gastric mucosa in the cervical esophagus
17	Pai et al. (63)	1997	Adenocarcinoma of cervical esophagus arising in aberrant gastric mucosa
18	Berkelhammer et al. (64)	1997	Gastric inlet patch containing submucosally infiltrating adenocarcinoma
19	Lauwers et al. (65)	1998	Adenocarcinoma of the upper esophagus arising in cervical ectopic gastric mucosa : rare evidence of malignant potential of so-called “inlet patch”
20	Klaase et al. (44)	2001	Heterotopic gastric mucosa of the cervical esophagus: a case of high-grade dysplasia treated with argon plasma coagulation and a case of adenocarcinoma
21	Pech et al. (66)	2001	Early stage adenocarcinoma of the esophagus arising in circular heterotopic gastric mucosa treated by endoscopic mucosal resection
22	Noguchi et al. (67)	2001	Primary adenocarcinoma of the cervical esophagus arising from heterotopic gastric mucosa
23	Chatelain et al. (23)	2002	Adenocarcinoma of the upper esophagus arising in heterotopic gastric mucosa : common pathogenesis with Barrett's adenocarcinoma?
24	Hirayama et al. (68)	2003	Endoscopic mucosal resection of adenocarcinoma arising in ectopic gastric mucosa in the cervical esophagus: case report

symptoms, signs, and pathomorphologic changes (see Table 2):

1. Asymptomatic carriers of esophageal HGM are classified as *HGM I*.
2. Symptomatic individuals with esophageal HGM complaining of dysphagia, odynophagia, or “extraesophageal manifestations” are classified as *HGM II* when morphologic changes are missing.
3. The smaller group of patients having additional morphologic changes (inlet patch complications), like esophageal strictures, stenoses, webs, or esophagotracheal fistula is addressed as *HGM III*.

4. The exceedingly rare cases with malignant progression of HGM should be subsumed under category *HGM IV* if dysplasia (intraepithelial neoplasia) is observed, or
5. Under category *HGM V*, if the diagnosis is invasive cancer.

Appending the suffix “a” is proposed to mark cases with a macroscopically visible inlet patch, whereas “b” should be used for only microscopic HGM.

Treatment

There are no standardized treatment strategies available for HGM and its complications. The clinicopathologic

Table 2. Clinicopathologic Classification of Esophageal Heterotopic Gastric Mucosa (HGM)

HGM I	Asymptomatic
HGM II	Symptomatic <i>without</i> morphologic changes (dysphagia/odynophagia)
HGM III	Symptomatic <i>with</i> morphologic changes (benign complications: strictures, ulcers, webs, stenoses, fistula)
HGM IV	Intraepithelial neoplasia (dysplasia) (low-grade/high-grade)
HGM V	Invasive adenocarcinoma
<i>Suffix</i>	
a.	= inlet patch (macroscopically visible patch of HGM)
b.	= microscopic foci (only microscopically visible HGM)

classification is proposed to define tailored treatment strategies, based on the limited current knowledge derived from the literature.

Asymptomatic patients with an incident finding of esophageal HGM (*HGM I*) don't require any treatment. The incident finding of an inlet patch raises the question if biopsy should be performed. Arguments would be, first to prove HGM histologically and second to rule out malignant progression (*HGM IV* and *V*). Evidence supporting this is missing. Adenocarcinoma in the cervical esophagus is rare whereas HGM is frequent. Incidence figures suggest that malignant transformation and progression to carcinoma is an exceedingly rare event and due to sporadic genetic alteration. The same line of evidence excludes an indication for endoscopic surveillance of HGM carriers. The main topic of intense controversial debate in Barrett's esophagus (47) needs not be a matter of discussion in HGM.

Symptomatic patients (*HGM II* and *III*) require medical therapy as primary mode of treatment. Formerly, inconsistent results have been achieved with application of the H2 blocker cimetidine (48) but complete symptom resolution has been reported by means of complete acid suppression with proton pump inhibition (49).

Benign complications as in *HGM III* (stenoses, webs, strictures) can be treated endoscopically, *e.g.*, by dilatation (10, 39), but biopsy is required to exclude malignant progression (*HGM IV* and *V*).

Special attention is needed when a stricture classified as benign (*HGM III*) is difficult to dilate. In this case, aggressive rebiopsy and perhaps prophylactic radical surgery has to be performed, as a malignant tumor can be missed on biopsy (39).

If the diagnosis is cancer, treatment has to be performed according to oncologic principles. Due to the lack of a standard strategy for this rare entity we suggest to adopt the same strategies as with squamous cell cancers of the cervical esophagus, rather than distal esophageal adenocarcinomas. For the oncologic strategy the localization of the tumor (cervical esophagus) appears more important than the histologic tumor type (adenocarcinoma).

How to treat dysplasia in HGM? The answer to this question is even more difficult since only few such cases have been reported so far (44–46). Endoscopic surveillance was suggested for cases with dysplasia (as well as cases with metaplasia (15)). Others applied local mucosal ablation by argon plasma coagulation (44, 46) and local resection after left-sided cervicotomy (44). Although the results reported were good, we question if these strategies should be recommended as standard approach. In Barrett's esophagus, HGD is an indication for surgery, because many of these patients are already harboring cancer (50). This should be considered when high-grade dysplasia in HGM is discovered and a treatment strategy is planned.

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