Aim of the study: Heteropic gastric mucosa of the upper esophagus (HGMUE) may be connected with disorders of the upper gastrointestinal tract, exacerbated by *Helicobacter pylori*. Furthermore, HGMUE may be the origin of malignant progression to cervical esophageal carcinoma.

Material and methods: In this work, 20 patients with diagnosed heteropic gastric mucosa of the upper esophagus (HGMUE) were subjected to 5-year follow-up to determine the extent and structure of histopathological changes within HGMUEs, as well as HGMUE dysplasia and metaplasia, and risk of their malignant transformation. As a diagnostic tool to describe localization, form, size and surface feature of HGMUEs, endoscopy was used. At the same time, the biopsies were collected for histopathological and microbiological analysis.

Results: In examined patients, HGMUEs were associated with inflammation, chronic gastritis, hiatus hernia, duodenal bulb erosion and ulcer and infection of *H. pylori*. Intestinal metaplasia and low grade dysplasia were also indicated. During 5 years of observation, both the clinical and histopathological image of diagnosed HGMUEs was stable. The patients with detected presence of *H. pylori* were treated with triple or quadruple therapy. These results show that HGMUEs may be associated with severe complications in the gastrointestinal tract, such as infection by *H. pylori*, hiatus hernia or duodenal ulcer. Although dysplasias and metaplasias found in diagnosed HGMUEs were not very numerous and relatively stable both clinically and histopathologically, at the present stage of the study we cannot exclude the possibility of HGMUE malignant transformation.

Key words: heteropic gastric mucosa, esophagus, metaplasia, dysplasia, malignant transformations.

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

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Introduction

Heteropic gastric mucosa of the upper esophagus (HGMUE), also termed “inlet patch”, is heteropic gastric mucosa (HGM) typically found in the esophagus. It is often characterized as a congenital asymptomatic anomaly. However, there are case reports showing that this lesion may play a role in the development of web, stricture, ulcer, perforation, or esophagotracheal fistula related to its capability of hydrochloric acid secretion [1–5]. These complications may be exacerbated by *Helicobacter pylori*, which colonizes 73% of “inlet patches” [6, 7]. Furthermore, HGMUE may be the origin of malignant progression to cervical esophageal carcinoma [8, 9]. Malignant progression of HGMUE occurs in a stepwise pattern, following the metaplasia-dysplasia-adenocarcinoma sequence [1, 9]. Despite the low incidence of clinically relevant manifestations of HGMUE, further studies are required to better understand its clinical significance [10].

The aim of this study was to evaluate the clinical features of 20 patients with diagnosed HGMUE, to determine prevalence of HGMUE dysplasia and intestinal metaplasia, to characterize the extent and structure of histopathological changes within HGMUE and, especially, to determine directions of these changes and risk of their malignant transformation during 5-year observation. The association of diagnosed “inlet patch” with *H. pylori* infection is also discussed.

Material and methods

In total, examinations were carried out in 1039 patients referred to the Endoscopy Ambulatory of Chair and Clinics of Internal Diseases, Angiology and Physical Medicine at the Silesian University of Medical Sciences in Bytom, from 1 September 2005 to 10 March 2006. In 20 of the examined patients 2–4 HGMUE were diagnosed. The mean age of patients with diagnosed HGMUE was 45.5 (from 18 to 67 years) and did not considerably differ from the mean age of all examined patients (46.7 years). The male : female ratio of patients with HGMUE was about 0.54 (7 : 13). All patients were carefully questioned about symptoms particularly involving upper esophageal and laryngopharyngeal regions.
Endoscopy was carried out using the video-gastroscopes GIF Q 145 and GIF Q 165, both made by Olympus Optical Co. Ltd (Tokyo, Japan), after standard premedication (topical 10% lidocaine spray) [11]. All detected HGMUEs were described in terms of localization, form, size and surface feature. Two to four biopsy specimens were obtained from each HGMUE as well as from the antrum and angular notch for urease test to determine the presence of H. pylori, as well as from associated mucosa lesions in the upper esophagus, as reference samples. All biopsy specimens were examined by a team of experienced histopathologists.

All patients with diagnosed HGMUEs were subjected to 5-year follow-up in the endoscopy ambulatory, finished in 2011. For diseases associated with HGMUE, these patients were treated according to the standard protocol. The patients with detected presence of H. pylori were subjected to 10-day eradication with triple therapy consisting of proton-pump inhibitors at two doses per day, metronidazole at a dose of 500 mg twice per day and amoxicillin at a dose of 500 mg three times per day [12]. From all 20 observed subjects, three control biopsies were collected: the first one during the first 9 to 13 months after HGMUE diagnosis, the second one within a period of 3 years (35–38 months) after this diagnosis, and the third one after 3 years following [12]. From all 20 observed subjects, three control biopsies were collected: the first one during the first 9 to 13 months after HGMUE diagnosis, the second one within a period of 3 years (35–38 months) after this diagnosis, and the third one after 5 years, at completion of follow-up. Two patients with diagnosed intestinal metaplasia and two others with dysplasia were examined by endoscopy every 6 months for the first 3 years and every 12 months later. By the term “dysplasia”, we mean a pathological, in some cases reversible state of epithelium, associated with cellular polymorphism, with disturbances of cell maturation and differentiation as well as with loss of basal cell polarity and of nucleus stratification. On the other hand, dysplasia, usually divided into low and high grade, is the most stable histological marker of premalignant states.

Each time, the sections from the antrum were collected for histopathological examination as well as for microbiological study to detect possible presence of H. pylori infection. When we did not obtain successful eradication of H. pylori with the standard protocol, we used quadruple protocols, with the use of clarithromycin or bismuth salts [12, 13].

Results

Heterotopic gastric mucosa of upper esophagiues were found in 20 patients from 1039 examinations. In the majority of patients, no special symptoms related to HGMUE were observed. Only one woman – a patient with diagnosed HGMUE – reported stomach itching and acidity sensation in the mouth with accompanying periodic sialorrhea, and one other patient was diagnosed due to the sensation of a foreign body in the esophagus which increased during swallowing.

The rate of endoscopic detection was determined as 19.2%. In general, HGMUE patches appeared as salmon-red lesions localized immediately below the upper esophageal sphincter. All HGMUEs appeared as oval patches with smooth and glossy surfaces that were discriminated from the surrounding esophageal mucosa by their well-defined margins. In the majority of patients (17 of 20) HGMUE lesions appeared as single patches and in 3 patients they were bifocal. The size of HGMUE patches ranged between 10 and 40 mm; in the majority of cases (18 of 23 patches; 81.8%) it was within the range 15–25 mm. Only in 3 patients was the size of “inlet patches” greater than 25 mm and in just one patient their diameter was less than 15 mm.

The results of histopathological examinations are shown in Table 1. Histopathological evaluation of 23 “inlet patches” revealed the presence of 17 patches of fundic type, 5 of antral type with noticeable parietal cells, and 1 patch of transitional (prepyloric) type. Inflammation was found in 16 of 23 detected HGMUEs; however, only one of these patches was infected with H. pylori. In 16 of 20 examined patients HGMUE was associated with chronic gastritis, in 8 with gastric infection of H. pylori, in 3 with duodenal bulb erosion, and in single cases with hiatus hernia and with duodenal ulcer. In 3 patients (15%) intestinal metaplasia in the stomach and in 2 patients (10%) atrophy of the mucosa was present. In 13 of the examined patients, a stomach infection of H. pylori was detected.

In 12 of 14 patients subjected to 10-day eradication using proton pump inhibitors, metronidazole and amoxicillin, the H. pylori gastric infection was eliminated. Efficiency of this antibacterial treatment protocol in these patients has been shown already during the first control endoscopy. The subsequent endoscopic analyses showed stable histopathological features of HGMUE and no reinfection of H. pylori in this group of patients. Apart from this, healing of all gastric and duodenal erosions as well as reduction of inflammat-

| Coexistence of Hp infection with 23 HGMUE ectopies in 20 patients | Histological type of gastric ectopy in upper esophagus | Presence of metaplasia/dysplasia and presence of Hp in HGMUE |
|---------------------------------------------------------------|------------------------------------------------------|----------------------------------------------------------|
| present | absent | intestinal metaplasia | low-grade dysplasia |
| 10 ectopies in 9 patients with Hp(+) | 7 ectopies with Hp(−) | 17 cases [1 case with Hp(+)] | 1 Hp(+) |
| 5 ectopies in 3 patients with Hp(+) | no ectopies with Hp(−) | 5 cases body type | 1 Hp(−) |
| 1 ectopy with Hp(+) | no ectopies with Hp(−) | 1 case prepyloric type | no Hp |

Hp – Helicobacter pylori
Acid secretion from parietal cells has also been demonstrated \[28–30\]. Conversely, the results of Poyrazoglu et al. [23] demonstrated the presence of parietal cells in HGMUEs, but no correlation between clinical symptoms and presence of these cells was found. This suggests that not only the presence but also the quantity of parietal cells is associated with HGMUE [23]. Furthermore, it was confirmed that symptoms are more marked in patients who have larger HGM patches [1, 31]. However, in the present study, there was no correlation between clinical symptoms and HGMUE size or type.

A strong affinity of *H. pylori* to colonize gastric type mucosa has been well demonstrated [6, 32–35]. In our research, colonization of HGMUE with *H. pylori* was not observed in the absence of this bacterium in the stomach, and such coexistence was observed only in one case. In fact, according to Borhan-Manesh and Farrum [34] and Gutierrez et al. [6] there is no correlation between positivity of *H. pylori* and inflammation in HGMUE patches. Whereas, we showed that the inflammatory process in HGMUE may be correlated with esophagitis, gastritis, or duodenitis, which may be severe complications of “inlet patches” [16, 35].

The question of malignant progression within HGMUE is controversial. The heterotopic, but otherwise not malignant epithelium may advance to invasive carcinoma following a metaplasia-dysplasia-carcinoma sequence [36]. Some authors [1] claim that the low frequency of malignant transformation of HGMUE as compared to Barrett’s esophagus suggests that it may not be regarded as a premalignant lesion. On the other hand, about 25 cases of adenocarcinoma which did not raise doubt to be developed from HGMUE were described [37–41]. Intestinal metaplasias have often been reported in association with adenocarcinoma developing in the inlet patch, but dysplasia has been reported only occasionally [42]. In our study, both metaplasia and dysplasia within HGMUE were found, contrary to the results of Tang et al. [16] and Akbayir et al. [17], who did not find metaplastic lesions in the HGMUE. Although these changes were not very numerous (about 12 and 9% for dysplasias and metaplasias respectively) and relatively stable, both clinically and histopathologically, at the present stage of the study, the possibility of malignant transformation within HGMUE cannot be excluded.

On the other hand, it is necessary to emphasize the advantages of endoscopy in combination with biopsy as a practical and safe method of inlet patch diagnosis [1, 11, 43–45]. This method is easy to carry out and repeat in ambulatory conditions and is well tolerated by patients. Due to its sensitivity to the mucosa, endoscopy is an effective tool for projecting deep mucosal visuals, allowing one to effectively evaluate the digestive system. It can also document diseases by generating three-dimensional images [19]. Thus, in our study we decided to use a method of endoscopic imaging allowing at the same time biopsies of gastrointestinal tissues for histopathological analysis.

In conclusion, the results of studies revealed that HGMUE should not be overlooked in the diagnostics. Although only severe symptomatic cases of this disorder require medical management, HGMUE may be associated with important complications in relation to gastric acid secretion, such as infection by *H. pylori*, hiatus hernia or duodenal ulcer, which should not be underestimated. Although the numbers of dysplasias and metaplasias in the diagnosed HGMUEs were limited (about 9 and 12%, respectively), and these lesions were relatively stable clinically, at the present stage of the study we cannot exclude the possibility of HGMUE malignant progression into adenocarcinoma. This may suggest the need for revision of the old paradigm of HGMUE as a benign and asymptomatic disorder. However, this question requires further studies.

On the other hand, the obtained results showed that the method of endoscopy combined with histopathological and microbiological analysis of biopsies is – due to its sensitivity, specificity and safety – a method “of choice” in clinical evaluation of metaplastic and non-metaplastic changes within HGMUE [43, 44].
The authors declare no conflict of interest.

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