

ORIGINAL ARTICLE

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Histopathological gastric mucosal changes in patients using proton pump inhibitors**Saadet Alan, Ayse Nur Akatli***Inonu University, Faculty of Medicine, Department of Pathology, Malatya, Turkey*

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Abstract

As a result of the widespread use of proton pump inhibitors (PPI), parietal cell hyperplasia/ hypertrophy (PCH/H) and a significant increase in fundic gland polyp (FGP) is observed in gastric mucosa in recent years. The aim of this study is to evaluate clinical and histopathological results of patients diagnosed with PCH/H and FGP. Clinical data and archived slides of 60 patients who were diagnosed with PCH/H or FGP at our institution between 2012-2019 were reviewed. Of the patients included in the study, 40 were women and 20 were men. Thirty-three cases, diagnosed with PCH/H and 27 cases diagnosed with FGP were investigated. H. Pylori gastritis was seen in 6 cases. In one case with a FGP, micronodular-linear neuroendocrine cell hyperplasia was observed. The FGPs, developing in the later stages of PPI use, are identified by endoscopic and pathological findings. Enterocromafin cell-like hyperplastic changes can become apparent in patients using PPI. H. Pylori gastritis was found to be less common in patients diagnosed with FGP and PCH/H than in the general population.

Keywords: Parietal cell hyperplasia, proton pump inhibitor, fundic gland polyp, neuroendocrine cell

Introduction

Proton pump inhibitors (PPI) are used for peptic acid-related diseases as the first-line treatment. In the last 20 years, these drugs have been used widely all over the world [1-3]. The suppression of gastric acid release by the long term use of PPI is reported to be associated with pneumonia, clostridium enteritis and osteoporosis [1]. After chronic PPI use, single-multiple small, exophytic, polypoid lesions often localized in the fundus or corpus of the gastric mucosa appear, and while these are usually asymptomatic, they are visible endoscopically [2,3]. Menegassi et al. showed PPI use to be associated with proliferative changes in the fundus and corpus mucosa, but the length of treatment that could provoke those changes was not determined [3].

Fundic gland polyps (FGP) are small exophytic and usually asymptomatic lesions. Histopathologically, dilated cystic glands usually lined with parietal and chief cells and occasionally mucous foveolar cells are seen. Dysplastic changes are rare [2,3]. These

polyps can occur in a sporadic or hereditary context. Hereditary cases are mainly associated with the Familial Adenomatous Polyposis Syndrome (FAP) and frequently multiple FGPs can be found in the gastric mucosa [2]. Sporadic FGPs are the most common type of gastric polyps. Prolonged use of PPI may result in parietal cell hyperplasia/hypertrophy (PCH/H), glandular lumen obstruction, and cystic dilatation of the glands. In fact, there are publications indicating that the incidence of FGP increases with the use of PPI. A negative relationship with *Helicobacter pylori* (*H.pylori*) infection was also noted [2-4].

As a result of the widespread use of PPI, PCH/H and a significant increase in FGP in the gastric mucosa have been observed in recent years. Because there is still controversy on the effects of PPI use, clinical and histopathological features of patients diagnosed with PCH/H, and FGP were evaluated in this study.

Materials and Methods

A retrospective analysis of the pathology files, diagnosed as PCH/H and/or FGP between 2012-2019 at the Pathology Laboratory of Inonu University Faculty of Medicine was performed. Ethics committee approval (2019/299) was obtained. A total of 60 patients with a histopathological diagnosis of PCH/H and FGP were reviewed based on histopathological examination and

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clinical information. Haematoxyline-Eosin and Giemsa stained slides were re-evaluated by two pathologists.

Results

Of the 60 patients in this study, 30 were PPI users according to the medical records. However, we were not able to determine whether the other 30 cases used PPI or not. Of the 30 PPI users, 19 were women and 11 were men. The mean age of the patients was 58.71(Table1). The mean age of women with PPI was 58.57 (23-92Y), and the mean age of men with PPI was 52.53 (18-78y). Histopathological evaluations determined parietal cell protrusions, PCH/H and occlusive glandular dilatation in oxyntic glands in all cases (Figure 1a,b).

Table 1. Age, sex and histopathological findings in patients with and without history of PPI use

Parameters	PPI + (n)	PPI-(n)
Gender		
Female	19	21
Male	11	9
Age		
<30	2	0
31-60	13	12
>61	15	18
Localisation		
Fundus	15	18
Corpus	11	9
Antrum	4	3
H.pylori		
Positive	4	2
Negative	26	28
Fundic gland polyp		
Positive	15	12
Negative	15	18

Morphological analysis showed a mixed cell population, which consisted of parietal, chief, and mucous neck cells lining the cysts and surface epithelium in FGP (Figure 1c,d). All patients were re-evaluated according to Sydney system. H.Pylori gastritis was seen in 6 cases. In one case using PPI, micronodular-linear neuroendocrine cell hyperplasia was observed within FGP (Figure 1d-f). Fundic gland polyps were seen in two FAP patients using PPI. In another FGP case, low grade dysplasia was observed in the epithelium. Fundic gland polyps were observed in half of the cases (15/30) known to be using PPI.

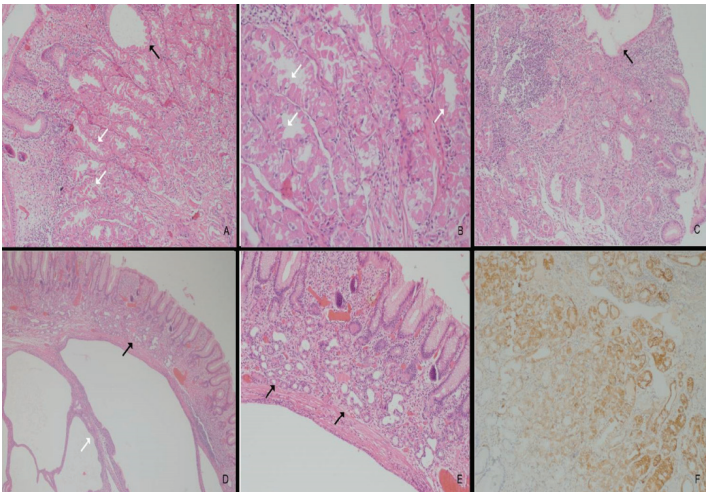


Figure 1. A-B Parietal cell hyperplasia/hypertrophy, parietal cell protrusion (white arrow), dilatation of oxyntic glands (black arrow), HE100, HE200. C: Parietal cell hyperplasia/hypertrophy, dilatation of oxyntic glands (black arrow), HE100 .D-E: glandular cystic dilatation in FGP (white arrow), micronodular-linear neuroendocrine cell hyperplasia (black arrow), HE100, HE200. F:Chromogranin A positivity in neuroendocrine cell hyperplasia area in FGP, HE200

Discussion

Fundic gland polyps can be defined in 0.8 to 23% of patients who underwent routine esophagogastric duodenoscopy, in various locations [5]. They are more common in middle aged women [2, 5]. Most of our cases with mucosal changes due to PPI were female and they had a mean age of 58.57 years. Graham first described the FGP in three patients using omeprazole, in 1992 [6]. As a result of the widespread use of PPI in recent years , many studies have reported an increase in the incidence of FGPs. The presence of such a relationship associated with the long-term use of PPI can cause anxiety for both physicians and patients [2]. Jalving et al. reported that patients using PPI for less than 1 year did not have an increase in the FGP frequency. However, long-term use of PPI has been found to increase the risk of FGP development by 4 times. There was no increase in the risk of dysplasia. It was observed that FGP development increased significantly in patients using PPI for more than five years [6,7]. However, an increase in FGP frequency with PPI use has not been observed in other studies.

Fundic gland polyps may be associated with congenital syndromes such as familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome, but it more often appears sporadically, constituting an incidental finding [5]. Sporadic FGPs are associated with PPI use in up to 23% [5]. Gastric polyps are seen in 30-100% of FAP patients. The majority (over 95%) of these are syndromic FGPs and the rest minority are adenomas with true malignancy potential [5]. Many studies have revealed frequent somatic mutations of the APC gene in FGPs associated with FAP. Although inactivation of the APC gene rarely happens in sporadic cases , mutations in β -catenin have been defined in sporadic multiple FGP [8-11] APC / β -catenin genes can cause parietal cell proliferation and may cause glandular obstruction and cyst formation by altering cell function [9]. In two of our patients using PPI, multiple FGPs were found to be associated with FAP syndrome.

The vast majority of FGP are small lesions that can be identified correctly on endoscopy, but the diagnosis should be confirmed pathologically [5,6]. FGP typically range from 1 to 8 mm in size, usually sessile and small. In our cases, the mean polyp size was 6,28 mm (3-10 mm). FGP can be single or multiple. In two cases, who were FAP cases, multiple polyps were reported in the mucosa. The polyps were often located in fundus and corpus in accordance with the literature. The suppression of peptic acid release by excessive PPI use, which causes significant changes in gastric mucosa, is frequently implicated in the literature. Gastritis or intestinal metaplasia may be accompanied [2,3,5]. Sporadic FGP are not associated with *H. pylori* infections, and an active infection can be protective against FGP. However, if active *H. Pylori* gastritis is detected, *H. Pylori* should be treated. [12]. *H. Pylori* gastritis was found in 10% of our cases. This situation was in accordance with the literature.

Cats et al., showed parietal cell proliferation, protrusions and glandular cystic dilatation in patients treated with chronic PPI. Histopathological changes in oxyntic mucosa were observed in 18% of the patients receiving short-term treatment and in 86% of the patients receiving treatment for more than one year [13].

Long-term acid suppression therapy induces obstruction of parietal cell canaliculi with hydrochloric acid, PCH/H and cytoplasmic protrusions. Increased intraglandular pressure results in cystic dilatation [2,9]. It has been reported that the formation of PPI-related FGP may be associated with a binary mechanism of cellular proliferation and obstruction of glandular secretion flow [2-4,9]. Histopathologically, dilatation of oxyntic glands, parietal cell protrusion and PCH/H were observed in all cases in this study.

The classical histological appearance of FGP, mixed cell population with disorganized glands, substantiated the classification of these lesions as hamartomatous lesions in the past. Brito et al. described in their study that the cysts in FGP were lined by a mixed cell population in 77% of the cases, [2]. Foveolar hyperplasia was only observed in 27% of the cases. In fact, proliferative changes in the foveolar epithelium are more related to chronic active gastritis and *H. pylori* infection. The presence of intraglandular mucous plugs and exfoliated cells supports the glandular flow obstruction hypothesis of FGP development [2-4].

According to Abraham, low-grade dysplasia is found only in 1% of sporadic FGP [14]. In this study, only 1 of the 27 cases demonstrated low grade dysplasia concomitant with FGP.

Several cases of neuroendocrine tumor development have been reported in patients using PPI [15,16]. Hypergastrinemia induces ECL cell hyperplasia and ECL cell carcinoids. Malignant transformation of a well differentiated type I gastric carcinoid has also been shown [16]. In one of our cases, micronodular-linear neuroendocrine cell hyperplasia was detected in a FGP. Because PPI use may raise the possibility of neuroendocrine cell hyperplasia and malignant transformation, patients using PPI should be investigated carefully with endoscopy for any suspicious lesions. If neuroendocrine cell hyperplasia is detected histopathologically, the question of which therapeutic modality should be chosen, and whether or not PPI should be stopped will remain unanswered. Further studies are required to determine the side effects of excessive PPI use.

Conclusion

In conclusion, gastric mucosal changes were evident in patients using PPI and the polypoid lesions developing in the later period, was supported by endoscopic and pathological findings. Enterochromaffin cell-like hyperplastic changes can become apparent in patients using PPI. Some of the cases were shown to have accompanying syndromic diseases. *H. Pylori* gastritis was found to be less common in patients diagnosed with FGP and PCH/H than the general population.

Competing interests

The authors declare that they have no competing interest.

Financial Disclosure

There are no financial supports.

Ethical approval

A retrospective analysis of the pathology files, diagnosed as PCH/H and/or FGP between 2012-2019 at the Pathology Laboratory of Inonu University Faculty of Medicine was performed. Ethics committee approval (2019/299) was obtained.

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