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Case Series

Two Cases of Increased Gastrointestinal Polyps in Familial Adenomatous Polyposis following Antiacid Agent Intake

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Keywords

Familial adenomatous polyposis · Fundic gland polyps · Colon adenoma · Proton pump inhibitor · Potassium-competitive acid blocker (vonoprazan)

Abstract

Introduction: Familial adenomatous polyposis (FAP), a hereditary disorder of the gastrointestinal tract, is an autosomal dominant inherited condition caused by germline mutations in the adenomatous polyposis coli (*APC*) gene. It is characterized by the development of hundreds to thousands of colorectal adenomatous polyps, which, if left untreated, can eventually develop into colorectal carcinomas. Representative extracolonic tumors in FAP include multiple duodenal adenomas and desmoid tumors. Moreover, multiple fundic gland polyps are frequently identified in the stomachs of patients with FAP. ***Case Presentation:*** Herein, we report the two cases. A 52-year-old woman who underwent total colectomy for FAP, and pancreatoduodenectomy was initiated on esomeprazole for the treatment of anastomotic erosion. Esophagogastroduodenoscopy performed 42 months later showed an increased number and size of gastric fundic gland polyps, which subsequently decreased after replacing esomeprazole with ranitidine. Similarly, a 39-year-old woman with FAP was initiated on vonoprazan for the treatment of reflux symptoms. Esophagogastroduodenoscopy and colonoscopy performed 14 months later indicated an increase in the number of gastric fundic gland polyps and colorectal polyps, which subsequently decreased after vonoprazan discontinuation. In these two cases, the increase and decrease in the number and size of fundic gland polyps and colon adenoma

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were associated with serum gastrin levels. ***Conclusion:*** Gastric fundic gland polyps and colon polyps may rapidly increase in number and size due to increased gastrin levels induced by proton pump inhibitor/potassium-competitive acid blocker use. Hence, these drugs should be prescribed with caution.

Introduction

Familial adenomatous polyposis (FAP) is one of the most well-known hereditary disorders of the gastrointestinal tract. It is an autosomal dominant inherited condition caused by germline mutations in the adenomatous polyposis coli (*APC*) gene. The main characteristic of FAP is the development of hundreds to thousands of colorectal adenomatous polyps. If left untreated, half of the patients with FAP eventually develop colorectal carcinoma by 40 years of age. Therefore, prophylactic colectomy is generally recommended as a treatment for these patients. Moreover, management of FAP using endoscopic polypectomy has been attempted in some patients with FAP who opt against prophylactic colectomy [1].

Owing to advancements in endoscopic resection methods, colorectal carcinoma-related mortality in patients with FAP can be reduced in the long term. Thus, clinical attention has recently been focused on managing the risk of extracolonic tumors in patients with FAP. Representative extracolonic tumors in FAP include multiple duodenal adenomas and desmoid tumors. Moreover, multiple fundic gland polyps (FGPs) are frequently identified in the stomachs of patients with FAP [2]. Herein, we report 2 cases of patients with FAP with FGPs and/or colon polyps, which were increasing in number and size due to the administration of proton pump inhibitors (PPIs) or potassium-competitive acid blockers (P-CABs).

Case Report

Case 1

A 52-year-old woman underwent total colectomy for FAP and pancreatoduodenectomy with pyloric ring preservation for intramucosal duodenal carcinoma at our hospital. Following these surgeries, she underwent esophagogastroduodenoscopy (EGD) and colonoscopy every 2 years. Treatment for erosion at the gastrointestinal anastomosis involved ranitidine 300 mg/day, a histamine blocker, and an antacid. In December 2012, the patient presented with anemia, accompanied by oozing from the erosions at the gastrointestinal anastomosis. During examination, multiple white FGPs, measuring 2–4 mm, were observed in the upper and lower parts of the gastric body (Fig. 1). Therefore, ranitidine was replaced with esomeprazole (20 mg/day), a PPI, which alleviated the patient's anemia (Fig. 1). In May 2016, 42 months after esomeprazole administration, surveillance EGD showed that the anastomotic erosion had disappeared. However, the FGPs had increased in size to a maximum diameter of 20 mm (Fig. 1). Histological examination of a biopsy specimen from a large FGP showed no malignant findings but indicated cystic dilatation of the fundic glands (online suppl. Fig. S1a; for all online suppl. material, see https://doi.org/10.1159/000538833) and approximately 5% Ki67-positive cells in the foveolar epithelium (online suppl. Fig. S1b). Moreover, the serum gastrin level was 43.7 pmol/L (normal range 11.9–46.9), and accordingly, on the higher side of the normal range due to PPI administration were diagnosed. Therefore, we administered ranitidine instead of esomeprazole. In January 2017, 5 months after transitioning to ranitidine

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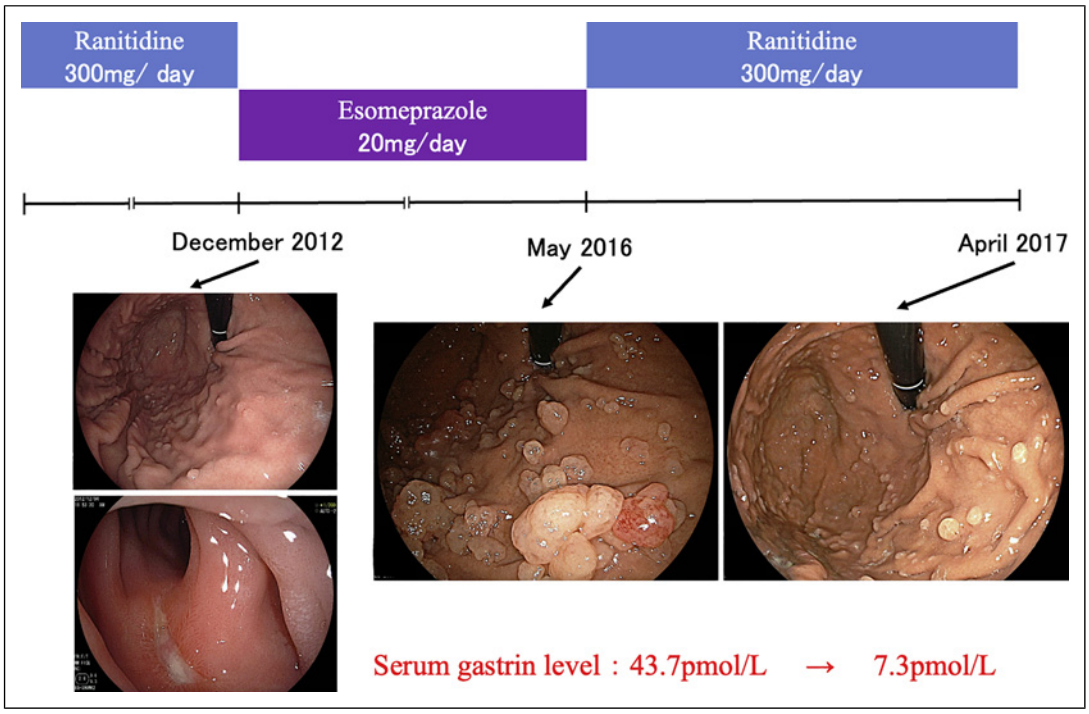

Fig. 1. Clinical course of case 1. History of antacid use. Endoscopic images of gastric fundic gland polyps before, during, and after taking esomeprazole (a PPI).

300 mg/day, the serum gastrin level decreased and normalized to 7.32 pmol/L. During this period, the EGD performed revealed a decrease in FGP number and size, with a maximum diameter of 4 mm. Histological examination of a biopsy specimen from an FGP showed reduced dilation of the fundic gland (online suppl. Fig. S1c) and fewer Ki67-positive cells compared to those observed during esomeprazole intake (online suppl. Fig. S1d). Anastomotic erosion at the gastrointestinal anastomosis remained absent (Fig. 1).

Case 2

A 39-year-old woman with FAP was being followed up with surveillance EGD and colonoscopy and had been treated for polyps by intensive endoscopic removal for decreasing the polyp burden (IDP) [3] yearly. She experienced acid reflux symptoms, including heartburn, chest pain, and nausea and started taking vonoprazan 20 mg/day in June 2021. In August 2022, 14 months after the initiation of vonoprazan, an increase in the number and size of FGPs and colon polyps were observed during surveillance EGD and colonoscopy, compared to those observed in the endoscopic findings in May 2021 (Fig. 2). Furthermore, the histopathological evaluation of biopsy specimens from the largest number of gastric polyps revealed cystic dilatation of the fundus gland. The superficial epithelium extending from the crypt exhibited cell proliferation with mild atypia (online suppl. Fig. S2a). Immunohistochemistry analysis of Ki67 revealed Ki67-positive cells, consistent with the atypical glands observed in hematoxylin and eosin staining (online suppl. Fig. S2b). Moreover, the serum gastrin level was as high as 42.4 pmol/L. Therefore, we recommended vonoprazan discontinuation and a follow-up. In January 2023, 5 months after vonoprazan discontinuation, the serum gastrin level decreased and normalized to 24.7 pmol/L. During this period, EGD and colonoscopy revealed a decrease in colon polyps and FGPs, with a maximum diameter of 4 mm (Fig. 2). In the pathological findings of FGPs after vonoprazan discontinuation, cell

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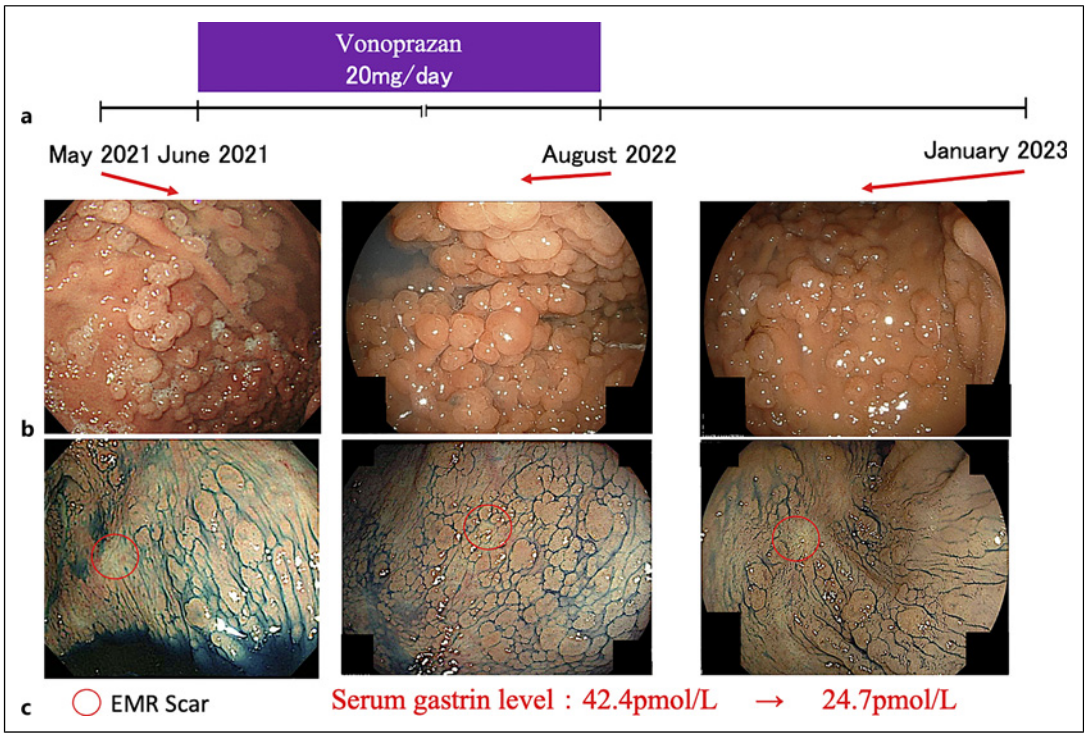

Fig. 2. Clinical course of case 2. **a** History of antacid use. **b** Endoscopic imaging of gastric fundic gland polyps before, during, and after administration of vonoprazan (a P-CAB). **c** Endoscopic imaging of colon polyps before, during, and after vonoprazan administration.

proliferation with mild atypia to the vicinity of the surface was still observed upon hematoxylin and eosin staining (online suppl. Fig. S2c), whereas the number of Ki67-positive cells decreased compared to that during vonoprazan intake (online suppl. Fig. S2d).

This study was approved by the Institutional Review Board of Hiroshima University Hospital (approval number: E2023-0151) and was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent. The CARE Checklist has been completed by the authors for this case report and is attached as online supplementary material.

Discussion

In the two cases presented in this study, we identified two clinical issues: the intake of PPI and P-CAB increased the number and size of FGPs, whereas the discontinuation of these drugs resulted in a decrease in the number and size of FGPs. Additionally, the increases and decreases in numbers and sizes of FGPs were associated with serum gastrin concentrations. Furthermore, the number of colonic polyps that developed in patients with FAP correlated with serum gastrin concentrations attributed to P-CAB intake.

Long-term PPI use is associated with increased FGPs [4]; patients who take PPIs for more than 1 year are at risk of developing FGPs [4]. However, the clinical significance of PPI-induced increase in FGPs remains unclear. Benign gastric polyps are often detected in healthy stomachs, with FGPs accounting for a significant proportion of these polyps. The increase in FGPs due to long-term PPI use is believed to be caused by parietal cell hyperplasia, which is

attributed to gastric acid suppression. Microscopically, FGPs that develop during PPI use exhibit increased and/or larger cysts, parietal cell hyperplasia, and parietal cell protrusions compared to those that develop without PPI use. Moreover, *Helicobacter pylori* infection is associated with the development of FGPs. Enzymatic degradation of gastric mucus by *H. pylori* proteases reportedly promotes gastric gland outflow, thereby preventing retention and cystic dilatation [5]. Therefore, the risk of FGP development is greater in *H. pylori*-negative patients, owing to the absence of this mechanism in their stomachs. In the present report, our cases showed that the intake of PPI/P-CAB was correlated with an increase in the number and size of FGPs; however, PPI use did not affect the prevalence of colonic polyps [6]. Moreover, the intake of PPI/P-CAB was correlated with an increase in the number of colon polyps, which could potentially be attributed to the underlying FAP.

Gastrin, a hormone primarily secreted by the G cells in the pyloric antrum of the stomach, binds to cholecystokinin B receptors and triggers histamine release from intestinal chromaffin cells. Additionally, it induces the insertion of an H^+/K^+ ATPase pump into the apical membrane of luminal cells. Gastrin and its derivatives are cell growth factors exerting anti-apoptotic and proliferative effects on the gastric epithelium. In an animal model, PPI-induced hypergastrinemia has been reported to enhance the proliferation of adenomatous cells [7]. Moreover, gastrin can promote the proliferation of human gastric and colon cancer cell lines [8, 9]. A clinical meta-analysis has reported that PPI use increases the risk of gastric cancer but not colorectal cancer [10]. In contrast, Abrahami et al. [10] suggested an increased risk of colorectal cancer associated with prolonged PPI use in a meta-analysis comparing PPIs and histamine-2 receptor antagonists [11]. Moreover, hypergastrinemia is associated with an increased risk of proximal- and intestinal-type gastric neoplasia [12]. Therefore, PPI-induced hypergastrinemia is associated with the development of gastric neoplasia and colorectal tumor. In our study, while the 2 patients with FAP taking PPI/P-CAB did not develop carcinoma, Ki67-positive cells in FGPs were observed to be larger during P-CAB intake than after discontinuation. However, no studies have examined the association between hypergastrinemia or PPI use and gastric or colorectal cancer. Moreover, it remains unclear whether PPI use plays a progressive or suppressive role in the carcinogenesis of gastric or colorectal cancers in patients with FAP. Hence, a comprehensive large-scale cohort study is essential to elucidate the potential risks of PPI use in patients with FAP.

To the best of our knowledge, none of the studies have investigated the association between the change in colorectal polyp numbers and oral PPI/P-CAB intake. Although total colectomy remains the first treatment of choice for patients with FAP, the usefulness of IDP for colon preservation has been recently reported. Hence, it is anticipated that fewer patients with FAP will undergo total colectomy. Therefore, the impact of oral P-CAB on patients with FAP with colon preservation, as in case 2, needs to be further investigated.

Statement of Ethics

This study was approved by the Institutional Review Board of Hiroshima University Hospital (approval number: E2023-0151) and was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Y.U. and H.I. conceived the idea of the study. A.I., S.I., K.I., and K.A. contributed to the interpretation of the results. Y.U. drafted the original manuscript. M.M. and S.O. supervised the conduct of this study. All the authors reviewed the manuscript draft and revised it critically on intellectual content. All the authors approved the final version of the manuscript to be published.

Data Availability Statement

The data supporting this article are available within the article itself and in its online supplementary material. Further inquiries can be directed to the corresponding author.

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