Successful treatment of proton pump inhibitor induced sporadic fundic gland polyps with an argon plasma coagulator in a patient with polycythemia vera

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1. Introduction

Fundic gland polyps (FGPs) are generally considered to be benign and the prevalence in patients undergoing upper endoscopy has been reported to be between 0.5% and 14% [1]. A recent study reported that long-term proton–pump inhibitor use increases the risk of FGPs [2]. There are two different types of FGPs: sporadic FGPs and FGPs in patients with familiar adenomatous polyposis (FAP) [3]. Although proton pump inhibitor (PPI) use is frequent, only a subset of patients develops multiple gastric polyps. While PPIs use is associated with the development of FGPs, discontinuation of PPIs is associated with regression of FGPs. Here, we report a rare case of non-respondent FGPs after discontinuation of PPI that were successfully treated using an argon plasma coagulator (APC).

2. Presentation of case

The patient was a 68-year-old woman with chronic epigastric pain who also had polycythemia vera. She had been taking 10 mg of omeprazole daily for the past three years for gastroesophageal reflux disease (GERD). An esophagogastroduodenoscopy (GF) and...
colonoscopy revealed over 100 pedunculated polyps in the gastric body and fundus (Fig. 1a). The antrum was normal. The size of the polyps was between 0.5 and 2.0 cm. Multiple biopsies of the polyps were taken. Histological examination of the specimens showed multiple fragments of fundic gland mucosa with dilated glands. The dilated gastric glands were lined by mucous neck and ballooned parietal cells. No mucosal inflammation, dysplasia, or Helicobacter pylori infection were observed (Fig. 2a, b). The immunohistochemical analysis showed that caudal-type homeobox 2 (CDX2)-negative cells were present in FGP (Fig. 2c). The colonoscopy revealed no significant findings. The patient’s past medical history included the use of rosuvastatin (2.5 mg, once daily) to treat hypercholesterolemia (serum cholesterol level: 272 mg/dl) for almost 4 years. Laboratory findings revealed leukocytosis of 15,400/mm3; red blood cell count (RBC) 5,780,000/mm3; platelet count 276,000/μl; aspartate aminotransferase (AST) 30 U/L; alanine aminotransferase (ALT) 38 U/L; lactate dehydrogenase (LDH) 316 U/L; alkaline phosphates (ALP) 390 U/L; triglycerides 150 mg/dl; total cholesterol 288 mg/dl; creatinine 0.7 mg/dl; creatinine phosphokinase (CPK) 393 U/L; blood urea nitrogen (BUN) 14 mg/dl; gastrin 92 pg/mL; prothrombin time 10.8 s; active partial prothrombin time 26 s; and fibrinogen degradation product 3.4 mg/mL. An abdominal computed tomography (CT) scan was negative for hemorrhage or infarction. During treatment for FGP, the patient was diagnosed with polythemia vera (PV) with a Janus kinase-2 (JAK2) V617F mutation and treated with ruxolitinib phosphate by the attending hematologist. Based on these findings and the clinical history, a diagnosis of FGPs with polycythemia vera was made.

Omeprazole use was subsequently discontinued. A repeat GF was performed 6 months and 1 year later and revealed a significant increase in the number and size of the polyps. We applied APC (ERBE USA Inc., Marietta, GA, USA) at 11/min and 40W over the FGP surface (Fig. 3a and b). During each GF, 50 ~ 100 FGPs were treated. APC treatment was performed every 6 months for almost 3 years, with 6 APC treatments in total. APC treatments resulted in a significant decrease in the size of the FGPs 4 years after discontinuing PPI (Fig. 1b–d). Pathology of biopsy specimens confirmed the presence of FGPs with no malignancy.

### 3. Discussion

FGP is defined as multiple fundic gland polyps in patients without an unusual adenomatous polyposis syndrome (FAP). They are commonly reported in patients in their 60s and predominantly in females. Jalving et al. reported that PPI therapy longer than 1 year is associated with a 4-fold increased risk of FGPs [3]. The mechanisms remain unknown. Genetic studies have shown that sporadic FGPs are linked to somatic mutations in the β-catenin gene and FAP-associated FGPs to germ-line mutations in the APC tumor suppressor gene [5]. Sporadic FRPs depend on activation of the β-catenin gene phosphorylation sites at exon 3 of the β-catenin gene [6]. Some groups have reported that morules associated with low grade dysplasia in FGPs might belong to the field of morules-associated tumors with wnt/β-catenin pathway disruption [7]. The β-catenin mutations in FGPs indicate a neoplastic nature, but it is known that FGPs have very limited malignant potential. CDX2 positivity in FGP morules has been correlated with β-catenin expression. However, CDX 2 was negative in this case.

Several authors have reported that parietal cell enlargement has been observed following long-term PPI treatment in both animals and humans [8]. Long-term treatment is associated with both a large cystic area and partial cell hyperplasia and protrusion. The increase in gastrin production secondary to acid suppression could cause the enlargement of parietal cells and decrease the number of chief cells without affecting A-like cells [9]. Otherwise evidence of gastrin acting as a growth factor is lacking. PPI induced FGPs

![Fig. 1. Gastroendoscopic study image of fundic gland polyps (FGPs).](image)
are not related to the level of hypergastrinemia [10]. A high level of serum gastrin (>400 pg/mL) suggests profound acid suppression. However, there does not seem to be any correlation between serum gastrin and the presence of FGP [11]. Mild hypergastrinemia is a physiological response to the reduction in gastric acid secretion. In the present study, serum gastrin level was within normal limits. Since the degree of hypergastrinemia does not differ between PPI users with and those without FRPs, other growth-promoting factors must play an important role in polyp development [10].

Sporadic polyps are found exclusively in patients without Helicobacter pylori (H. pylori) infection [10]. The absence of H. pylori is strongly associated with the presence of FGP. Some mechanisms have been proposed that suggest a protective effect with Helicobacter pylori [10,12]. However, H. pylori was not found in our case.

In patients treated with PPI, large numbers of polyps can exist, and these regress with discontinuation of PPI therapy [13]. Large polyps should be removed to confirm their diagnosis because fundic polyps rarely exceed 1 cm in diameter [14]. In particular, cases of polyps larger than 1 cm, ulceration, and unusual location such as the antrum, should prompt a more aggressive approach [15].

APC has evolved and several application modes are available, these include: forced and pulsed with various coagulation effects [16]. APC delivers monopolar energy through ionized argon gas. APC damage is limited to the superficial layers and ranges from treated areas with higher resistance to untreated area with a lower resistance, which protects against perforation by deep burn [17,18]. APC is irreplaceable for destroying adenomatous remnants from endoscopically resected polyps, particularly when piecemeal resection takes place, as APC reduces the relapse rate with no associated complications [19].

The prevalence of gastrointestinal lesions is higher in PV patients than in the general population and PV is a risk factor for gastroduodenal lesions [20]. In particular, gastric erosion or ulcers are frequency observed in PV patients. The pathogenetic mech-
anism responsible for gastroduodenal lesions possibly involves blood flow due to increased plasma viscosity, hyperhistaminaemia, and trophism [20]. PPI use is a strong risk factor for the development of FGPs and discontinuation of PPI is associated with regression of FGPs, but not in the present case. Blood hyperviscosity or other factors might play a role in the growth and continual development of FGPs after cessation of PPI in patients with PV. However, the mechanism involved in the interaction between FGP and polycythaemia vera remains unknown.

4. Conclusion

We conclude that PPI use is a strong risk factor for the development of FGPs and discontinuing PPI is associated with regression of FGPs, but not in patients with polycythaemia vera. A rare case of non-respondent FGPs after discontinuation of PPI was successfully treated using an APC. The mechanism involved in the interaction between FGP and polycythaemia vera remains unknown.

Conflicts of interest

None of the authors have identified a conflict interest.

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Ethical approval

This study was approved by our hospital’s institutional review board.

Consent

Written informed consent was obtained from the patient’s relatives for publication of this manuscript and any accompanying images. Copies of the written consent are available for review by the Editor-in-Chief of this journal.

Author contributions

Dr. Kato had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: Kato, Onodera
Acquisition of data: Kato, Ki, Taniguchi
Analysis and interpretation of data: Kato, Taniguchi
Drafting of the manuscript: Kato, Onodera

Guarantor

Dr. Kato had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

[1] S.W. Camack, R.M. Genta, C.M. Schuler, M.H. Saboorian, The current spectrum of gastric polyps: a 1-year national study of over 120,000 patients, Am. J. Gastroenterol. 104 (2009) 1524–1532.
[2] M. Jalgving, J.J. Koornstra, J. Wesseling, H.M. Boesen, S. De Jong, J.H. Kleibeuker, Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy, Aliment. Pharmacol. Ther. 24 (2006) 1341–1348.
[3] G. Bertoni, R. Sassatelli, E. Nigrisoli, M. Pennazio, P. Tansini, A. Arrigoni, et al., Dysplastic changes in gastric fundic polyps of patients with familiar adenomatous polyposis, Ital. J. Gastroenterol. Hepatol. 31 (1999) 192–197.
[4] R.A. Agha, A.J. Fowler, A. Saeta, I. Barai, S. Rajmohan, D.P. Orgill, S. Group, The SCARE statement: consensus-based surgical case report guidelines, Int. J. Surg. 34 (2016) 180–186.
[5] S.C. Abraham, S.J. Park, L. Murgatesgui, S.R. Hamilton, T.T. Wu, Sporadic fundic gland polyps with epithelial dysplasia: evidence for preferential targeting for mutations in the adenomatous polyposis coli gene, Am. J. Pathol. 161 (2002) 1735–1742.
[6] M. Torbenson, J.H. Lee, M. Cruz-Corrales, Q.W. R.Avic, K. Rastgar, S.C. Abraham, et al., Sporadic fundic gland polyposis: a clinical, histological, and molecular analysis, Mod. Pathol. 15 (2002) 718–722.
[7] G.D. Petris, L. Chen, Morules in fundic gland polyps: a case report, Int. J. Clin. Exp. Pathol. 7 (2014) 1241–1245.
[8] D.K. Driman, C. Wright, G. Tougas, R.H. Riddell, Omeprazole produces partial cell hypertrophy and hyperplasia in humans, Dig. Dis. Sci. 41 (1996) 2039–2047.
[9] T. Masaoaka, H. Suzuki, T. Hibi, Gastric epithelial cell morphology and proton pump inhibitor, J. inhibitor. Clin. Biochem. Nutr. 42 (2008) 191–196.
[10] B. Foissner, C.S. Juanu, T.C. Martinu, G. Qigutd, U. Syversen, H.L. Waldum, Serum gastrin and chromogranin level in patients with fundic gland polyps caused by long-term proton pump inhibition, Scand. J. Gastroenterol. 43 (2008) 20–24.
[11] M. Hongo, K. Fujimoto, Gastric Polyp Study Group, Incidence and risk factor of fundic gland polyps and hyperplastic polyps in long-term proton pump inhibitor therapy: a prospective study in Japan, J. Gastroenterol. 45 (2010) 618–624.
[12] A. Zelter, J.L. Fernandez, C. Bilder, P. Rodrigues, A. Wonaga, F. Dorado, Fundic gland polyps and association with proton pump inhibitor intake: a prospective study in 1,780 endoscopies, Dig. Dis. Sci. 56 (2011) 1743–1748.
[13] J.S. Kim, H.S. Chea, H.K. Kim, Y.S. Cho, Y.W. Park, H.S. Son, et al., Spontaneous resolution of multiple fundic gland polyps after cessation of treatment with omeprazole, Korean J. Gastroenterol. 51 (2008) 305–308.
[14] S.W. Carmacks, R.M. Genta, D.Y. Graftham, C.Y. Lawson, Management of gastric polyps: a pathology-based guide for gastroenterologists, Nat. Rev. Gastroenterol. Hepatol. 6 (2009) 331–341.
[15] Y.H. Shabi, M. Rugge, D.Y. Graham, R.M. Genta, Management of gastric polyps: an endoscopic approach, Clin. Gastroenterol. Hepatol. 11 (2013) 1374–1384.
[16] H. Mnar, A. Hay, M. Faeder, O. Pech, N. Plum, C. Eil, The tissue effect of second generation argon plasma coagulation (VIO APC) in comparison to standard APC and Nd: YAG laser in vitro, Acta Gastroenterol. Belg. 70 (2007) 352–356.
[17] J.P. Watson, M.K. Bennett, S.M. Griffin, K. Mathewson, The tissue effect of argon plasma coagulation on esophageal and gastric mucosa, Gastrointest. Endosc. 52 (2000) 343–345.
[18] W. Johans, W. Liu, J. Janssen, S. Kahl, L. Greiner, Argon plasma coagulation (APC) in gastroenterology experimental and clinical experience, Eur. J. Gastroenterol. Hepatol. 9 (1997) 581–587.
[19] J.C. Broker, B.F. Saunders, S.G. Shah, C.J. Thapar, N. Suzuki, C.B. Williams, Treatment of argon plasma coagulation reduces recurrence after piecemeal resection of large sessile colonic polyps: a randomized trial and recommendations, Gastrointest. Endosc. 55 (2002) 371–375.
[20] G. Torgano, C. Mandell, P. Massaro, C. Abbati, A. Ponzetto, G. Bertinieri, et al., Gastroduodenal lesions in polycythaemia vera: frequency and role of helicobacter pylori, Br. J. Haematol. 117 (2002) 198–202.

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