〈Case Report〉

A patient with achalasia bleeding from a hyperplastic polyp caused by long- term oral administration of gastric acid secretion inhibitors after per-oral endoscopic myotomy

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ABSTRACT Since gastroesophageal reflux disease occurs in a certain percentage of patients with esophageal achalasia after per-oral endoscopic myotomy (POEM), long-term administration of gastric acid secretion inhibitors is required in some cases. Prolonged use of gastric acid secretion inhibitors is associated with the development of gastric polyps, including hyperplastic polyps. This study reports the case of a 70-year-old female with esophageal achalasia and bleeding from gastric hyperplastic polyps after POEM, followed by long-term administration of gastric acid secretion inhibitors to prevent reflux esophagitis. One month after the surgery, she took potassium competitive acid blocker (P-CAB). She had no more heartburn symptoms. She decided to stop taking P-CAB on her own. Three months later, symptom of heartburn became severe, and she underwent esophagogastroduodenoscopy (EGD), which showed Los Angeles classification grade C reflux esophagitis. Administration of P-CABs was resumed and the reflux esophagitis resolved rapidly, but despite continued administration of P-CAB, the anemia progressed after 4 years. EGD results showed that the reflux esophagitis had resolved, but bleeding from a newly developed hyperplastic polyp was noted after P-CAB administration.

doi：10.11482/KMJ-E202551071 *(Accepted on February 15, 2025)*

Key words：Gastric acid secretion inhibitors, Hyperplastic polyp, Esophageal achalasia, Per-oral endoscopic myotomy

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INTRODUCTION

Treatments for esophageal achalasia have historically included medical therapy, balloon dilatation, and Surgery. In 2008, Inoue *et al*, first reported per-oral endoscopic myotomy (POEM) for the endoscopic treatment of esophageal achalasia[1]. Since then, POEM has been performed at many institutions in Japan and abroad. It has been reported that approximately 60% of patients develop reflux esophagitis after treatment with POEM[2] and gastric acid secretion inhibitors are often required to treat or prevent reflux symptoms. However newly developing gastric polyps due to long-term administration of proton-pump inhibitors (PPIs) and potassium-competitive acid blockers (P-CABs) have been reported[2], and there have been case reports of patients bleeding from gastric polyps caused by long-term administration of gastric acid secretion inhibitors[3-6]. We report a suggestive case of an esophageal achalasia patient with bleeding from a hyperplastic polyp following long-term administration of P-CAB for reflux esophagitis after POEM treatment, and review related literature.

CASE REPORT

A 70-year-old female patient underwent Heller myotomy for esophageal achalasia at the age of 40 years at another hospital. Thereafter her symptoms of dysphagia improved, with long-term stable clinical status and no flare-ups. However, at the age of 70 (30 years after the surgery), she again experienced postprandial reflux symptoms and was referred to our hospital. The patient had a history of ruptured right middle cerebral artery aneurysm (in her 40s) and dyslipidemia (in her 30s), and was prescribed pregabalin 50 mg/day, rosuvastatin calcium 5 mg/day, eldecalcitol 0.75 μg/day, limaprost alfadex 15 μg/day, and urapidil 60 mg/day for the underlying disease. She had no history of smoking or alcohol consumption. Symptoms were mainly nausea, vomiting, and lethargy during and after meals, with Eckardt symptom score of 0 and GSRS score of 23. There were also no abnormal findings on physical examination as well as no abnormal hematological findings. A non-contrast computed tomography scan of the chest and abdomen showed no abnormal organic diseases causing symptoms. Esophagogastroduodenoscopy (EGD) revealed that the lower esophageal sphincter (LES) was severely constricted and the mid-esophagus dilated (Fig. 1a). Barium contrast shows barium stasis in lower esophagus (Fig. 2a). High-resolution manometry (HRM) showed low LES pressure but no swallowing relaxation, and peristaltic

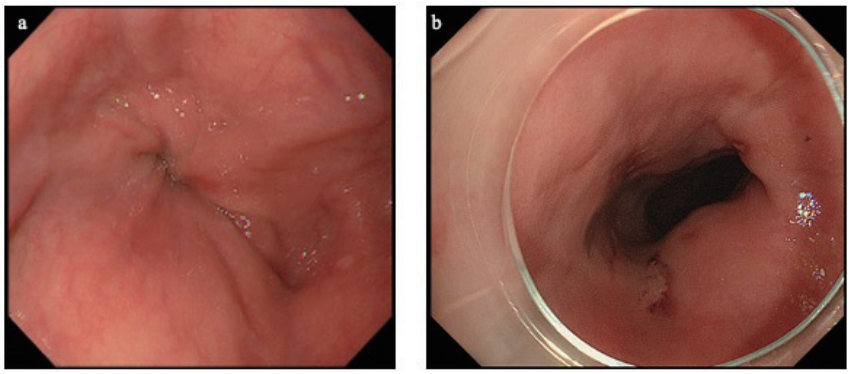

Fig. 1. Esophagogastroduodenoscopy image
a before peroral endoscopic myotomy (POEM) treatment
b after POEM treatment.

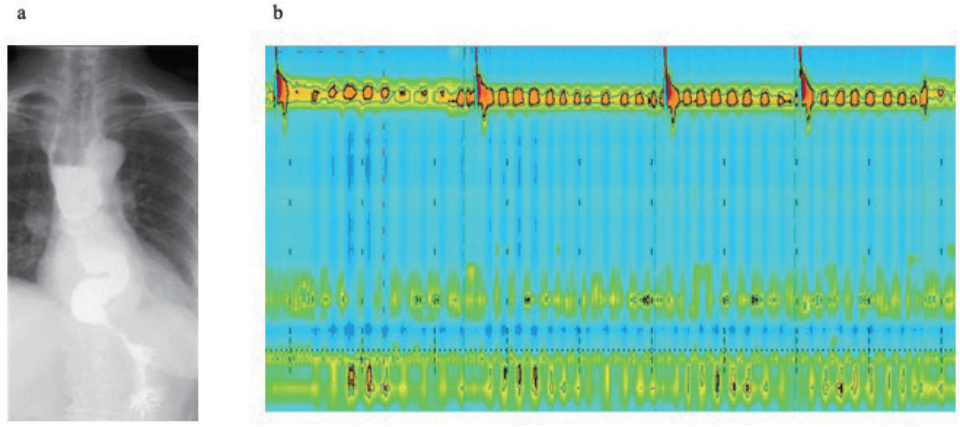

Fig. 2.
a Barium contrast study before POEM treatment. The esophagus was tortuous, and barium stagnation was observed in the lower esophagus.
b High-resolution manometry (HRM) before POEM treatment, showing low lower esophagus sphincter (LES) pressure but no swallowing relaxation and disappearance of peristaltic waves in the esophageal body.

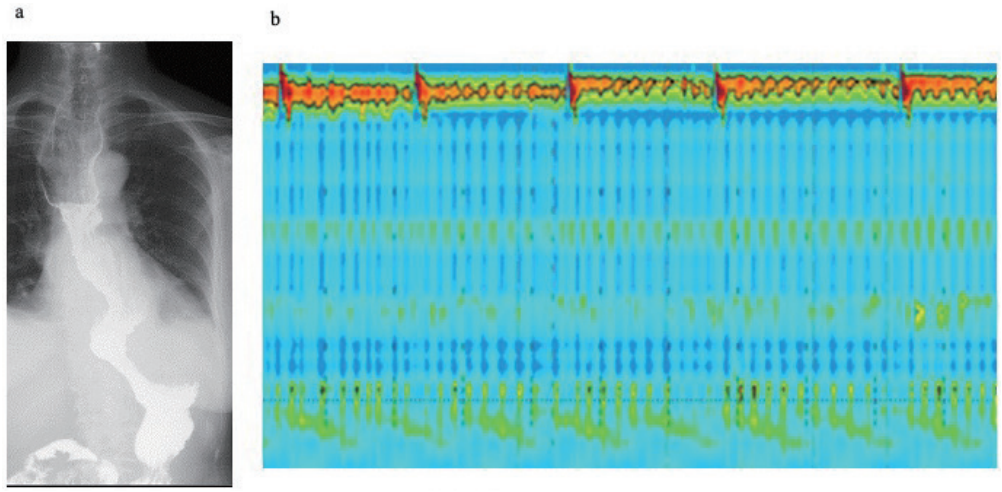

Fig. 3.
a Barium contrast study after POEM treatment. Barium stagnation was not observed.
b HRM after POEM treatment. LES pressure was lower than before treatment.

waves in the esophageal body were absent (Fig.2b). Based on these results, we diagnosed a recurrence of esophageal achalasia Type II and determined that additional treatment was necessary due to the strong symptoms. POEM treatment for esophageal achalasia, and postoperatively, the hypercontractility of the lower esophagus improved and barium was able to pass into the stomach (Fig. 1b and 3a). LES pressure was also reduced on HRM compared to before POEM treatment (Fig. 3b). The patient had been taking P-CAB (vonoprazan) for one month postoperatively to prevent reflux esophagitis, but stopped at her own discretion when she no longer had heartburn symptoms. Three months later, she developed severe heartburn symptoms and underwent EGD, which revealed severe reflux

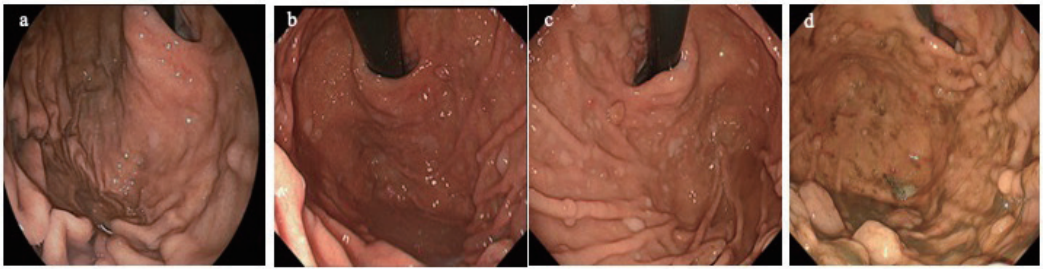

Fig. 4.
a Esophagogastroduodenoscopy before starting potassium-competitive acid blocker (P-CAB) administration.
b Esophagogastroduodenoscopy 6 months after starting P-CAB administration.
c Esophagogastroduodenoscopy 1 year after starting P-CAB administration.
d Esophagogastroduodenoscopy 3 years after starting P-CAB administration. New fundic gland polyps were observed.

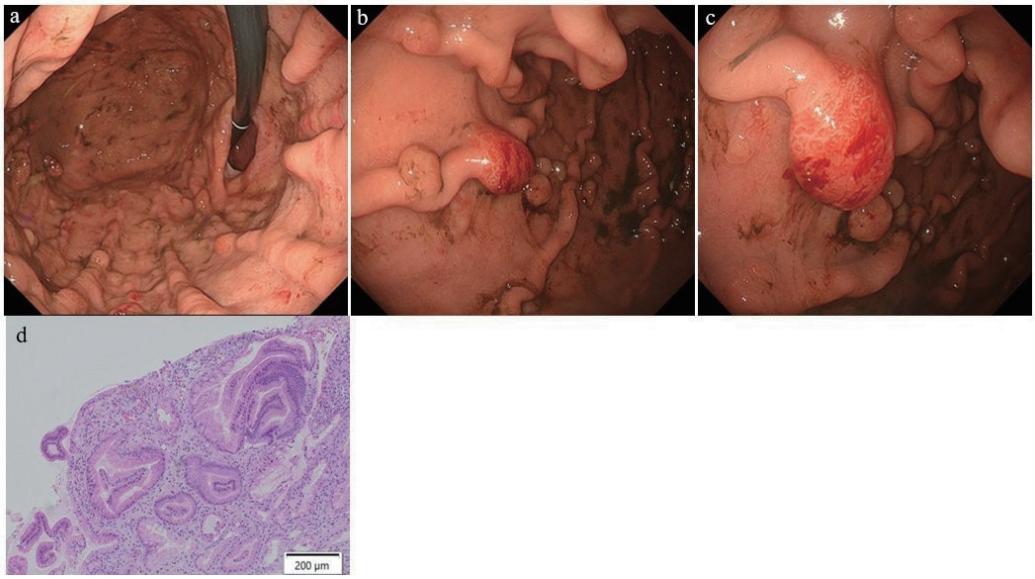

Fig. 5.
a Esophagogastroduodenoscopy 4 years after the start of P-CAB administration.
b Bleeding from a newly arising hyperplastic polyp (distant view).
c Bleeding from a newly arising hyperplastic polyp (near view).
d Histopathology was consistent with a hyperplastic polyp (HE stain, 10×).

esophagitis of Los Angeles Classification grade C. P-CAB administration was resumed and reflux symptoms improved rapidly. She had been taking a PPI (lansoprazole) for some time because of hypergastrinemia (blood gastrin level 798 pmol/L), but because of worsening heartburn symptoms in a few weeks, she returned to P-CAB 20 mg/day and continued treatment. Thereafter, the patient was followed up with annual EGD once a year, which showed that although reflux esophagitis had gradually healed, multiple new polyps were found in the fundic gland (Fig. 4a-c). In addition, the anaemia, which originally remained around Hb 13.0 g/dL, gradually progressed to Hb 11.5 g/dL six months after the start of P-CAB administration, Hb 11.0 g/dL one year later and Hb 9.7 g/dL two

years later. There were no lesions that could be a source of haemorrhage and the patient was followed up with iron administration and improved to Hb 14.0 g/dL after one and a half months. However, three years after P-CAB administration, anaemia progressed again to Hb 11.1 g/dL. EGD revealed a dark-brown residue in the stomach, but there was no lesion that could have been a source of bleeding (Fig. 4d), and she continued to be followed up with iron administration. However, four years after the start of P-CAB treatment, anaemia progressed to Hb 9.0 g/dL. EGD showed bleeding from part of some new polyps (Fig. 5a, b, and c). The bleeding polyp was biopsied and found to be a hyperplastic polyp (Fig. 5d). Endoscopic resection of hyperplastic polyps plus additional anti-reflux surgery was proposed to the patient but declined. Currently, her anemia is improving with the administration of iron supplements, and given her age and general condition, she continues to be managed conservatively.

DISCUSSION

POEM is a safe and effective treatment, but postoperative reflux esophagitis may rarely occur. Shiwaku, *et al.*[7] reported 1,346 patients who underwent a POEM procedure in Japan. They found no serious complications in all cases and reflux esophagitis in approximately 60% (grade A 33%, grade B 24%, grade C 6%, grade D 0.2%), all of which were well controlled by gastric acid secretion inhibitors. Among patients who must take acid secretion inhibitors for a long period of time, bleeding from newly developed gastric polyps may occur, as in the present case, although it is rare (Table 1). A PubMed search using the keywords "PPI," "gastric polyp," and "bleeding" revealed that the shortest duration of bleeding was less than 1 year, there was no common risk of underlying diseases or other background factors, and no clear causal relationship was identified regarding the duration of administration or total dose. In patients with esophageal achalasia, severe forms of reflux esophagitis will develop once gastroesophageal acid reflux occurs after POEM due to the loss of peristaltic waves in the body of the esophagus. Therefore, long-term administration of PCAB is necessary. One of the gastric mucosal changes associated with long-term administration of acid secretion inhibitors is the appearance of hyperplastic

Table 1. A case of bleeding from a gastric polyp caused by long-term administration of a gastric acid secretion inhibitor

reporting year	reporter	age & sex	type and dosage of gastric acid secretion inhibitors	Projections and periods	Primary disease	Types of polyps	Infection of *H. pylori*	Blood gastrin level (pmol/L)	outcome
1994	Handa, *et al* [4]	60s F	OPZ 20mg/day	1 year	scleroderma	Hyperplastic	−	96	Improved by reduse of PPI
2015	Kawaguchi, *et al* [5]	60s M	PPI (details unknown)	unknown	alcoholic cirrhosis, HCC	Hyperplastic	+	167	Improved by endoscopic resection
2017	Takeda, *et al* [6]	40s M	LPZ 15mg/day	10 years	HT, depression	Fundic gland	+	43	Improved by endoscopic resection and discontinuation of PPI
2020	Farooq, *et al* [7]	60s M	PPI (details unknown)	7 years	HT, DM	Hyperplastic	−	NA	Improved by endoscopic resection
2021	Kusano, *et al* [8]	80s F	LPZ 15mg/day	3 years	HT, DM, HL	Hyperplastic	−	NA	Improved by change of PPI to H_2-blocer
2023	our case	70s F	Vonoprazan 20mg/day	4 years	HT, RAA	Hyperplastic	−	798	Progress without recurrence with iron administration

OPZ: omeprazole, LPZ: lansoprazole, HCC: hepatocellular carcinoma, HT: high blood pressure, DM: diabetes, HL: hyperlipidemia, RAA: raptured cerebral aneurysm

polyps, from which bleeding has been reported, but there are no reports of bleeding due to long-term administration of acid secretion inhibitors after POEM treatment. However, we should consider the possibility of situations where the polyp is gradually bleeding because of gastric wall contractions but this has not been revealed at the time of endoscopy. Although the mechanism of hyperplastic polyps induced by long-term PPI administration is unknown, histopathological findings suggest that the development of hyperplastic polyps is caused by an abnormal proliferation of regenerative neointimal ducts in atrophic mucosa[8]. The patient was *H. pylori*-negative and had no atrophy of the gastric mucosa, and the chronological history, suggesting that long-term administration of PPIs and P-CABs led to a hypoacidity state and secondary hypergastrinemia, which created an intragastric environment conducive to the formation of hyperplastic polyps. Compared with existing reports, the hypergastrinemia was more pronounced in this patient, which may be due to the underlying diabetes mellitus and reduced renal function (creatinine level 0.91 mg/dL, eGFR 45 mL/min/1.73 m^2 at the first visit to our hospital), which may have contributed to the reduced gastrin resolution. In the present case, it was not possible to change or reduce the dose of gastric acid secretion inhibitors because the symptoms recurred after the discontinuation of P-CAB. Given the patient's age and general condition, conservative management was chosen because the patient did not agree to aggressive endoscopic treatment such as polypectomy or additional anti-reflux surgery, and because the anemia improved only with the administration of iron supplements. However, aggressive endoscopic treatments should be considered when bleeding is poorly controlled. In the future, it will be necessary to clarify the characteristics of cases in which anti-reflux surgery should be added to POEM. If anemia develops during treatment with gastric antisecretory agents, endoscopy should be performed, the possibility of bleeding from newly developed gastric hyperplastic polyps should be considered, discontinuation of gastric antisecretory agents should be also considered, and polypectomy or additional antireflux surgery should be considered if necessary.

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