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• *CASE REPORT* •

Effect of *Helicobacter pylori* eradication on gastric hyperplastic polyposis in Cowden's disease

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Abstract

A 21-year-old woman with complaints of hematochezia was diagnosed as having Cowden's disease (CD), an autosomal dominant condition characterized by multiple hamartomas, since facial papules and gingival papillomas were identified. On endoscopy, multiple hyperplastic polyps were seen in the rectum and left-side colon. There were also esophageal glycogenic acanthosis and hyperplastic polyposis in the antrum accompanied by *Helicobacter pylori*-related gastritis. Although gastric hyperplastic polyposis had by no means regressed with unsuccessful first-line eradication therapy for *H pylori*, following cure of the infection with salvage therapy consisting of rabeprazole, amoxicillin and metronidazole, the polyposis lesions almost disappeared. Follow-up gastroscopy 2 and 3 years after cessation of the second-line eradication therapy revealed almost complete regression of the polyposis lesions with no evidence of *H pylori* infection. We recommend eradication treatment for CD patients with gastric hyperplastic polyps and the infection, as the occurrence of gastric carcinoma among hyperplastic polyps has been described.

Key words: Cowden's disease; *Helicobacter pylori*; Hyperplastic polyposis

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INTRODUCTION

Cowden's disease (CD) is a rare autosomally dominant inherited cancer predisposition syndrome characterized by multiple hamartomas involving various organ systems derived from all three germ cell layers[1]. Pathognomonic mucocutaneous features include facial papules that are especially prominent around the nasal labial folds and perioral area; acral keratoses of the palms and soles; and mucous papillomas[1,2]. Alimentary tract abnormalities found in CD primarily appear as multiple polyps of various histopathologic features including hamartomatous, hyperplastic, inflammatory, juvenile, lymphomatous and adenomatous polyps[3-6]. Hyperplastic polyp is the most common gastric polyp seen in CD[6].

Although hyperplastic polyp itself is non-neoplastic, the risk of dysplastic changes and/or carcinomatous conversion is now recognized[7]. Patients with gastric polyps may present with bleeding, abdominal pain or gastric outlet obstruction[8]. Therefore, most clinicians agree that the large gastric polyps or polyps associated with complications should be removed endoscopically or surgically[9]. Recently, the strong relationship between gastric hyperplastic polyp and *Helicobacter pylori* (*H pylori*) infection has been demonstrated[10-13]. Ohkusa *et al* [10] reported that most hyperplastic polyps disappeared after cure of the infection. Eradication of *H pylori* may, therefore, be a therapeutic option for hyperplastic polyps occurring in association with *H pylori* gastritis[10-12]. Herein, we describe a patient with CD in whom hyperplastic gastric polyposis with concomitant *H pylori* infection almost disappeared following successful eradication.

CASE REPORT

A 21-year-old Japanese woman presented with hematochezia of 2-wk duration. The past and family histories were unremarkable. Laboratory tests were normal except for positive fecal occult blood. On physical examination with dermatological consultation, multiple facial papules and gingival papillomas were identified. Thus, a definite diagnosis of CD was made, fulfilling the two major clinical criteria[14]. However, no abnormalities involving the thyroid, breast, skeleton and genitourinary tract were found. Upper gastrointestinal endoscopy revealed numerous sessile or hemispheric polyps up to 5 mm in size within the antrum (Figure 1). Biopsies obtained from the polyposis revealed hyperplasia of foveolar epithelium, along with neutrophil and mononuclear cell infiltration, consistent with histological characteristics of hyperplastic polyp[11]. In addition, multiple, whitish, minute protrusions, which showed positive staining

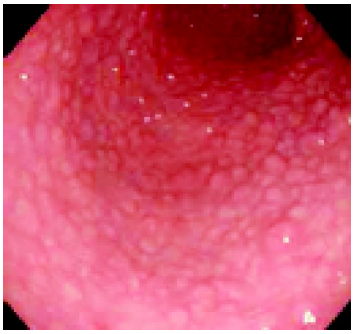

Figure 1 Endoscopy revealed numerous sessile polyps up to 5 mm in size within the antrum.

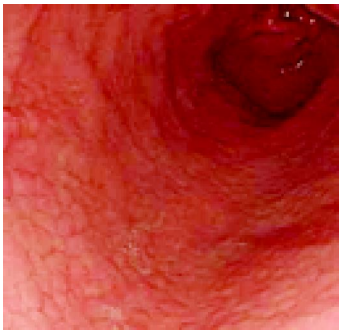

Figure 2 Note the near disappearance of polyposis on repeat gastroscopy 2 years after the commencement of anti-*Helicobacter pylori* second-line therapy.

with iodine, were observed throughout the esophagus. Biopsies from these lesions showed glycogenic acanthosis. Colonoscopy showed multiple, whitish, sessile polyps ranging in size from 2 to 8 mm, which extended from the rectum to the descending colon but exhibited a predilection for the rectosigmoid area. These polyps were histopathologically judged to be hyperplastic. Barium contrast study of the small bowel and computed tomograms of the brain, neck, chest, abdomen and pelvis showed no abnormalities.

H pylori infection was detected both in the antrum and corpus by Giemsa staining and rapid urease test using biopsy samples obtained during gastroscopy. The patient was treated with a 1-wk course of triple therapy consisting of lansoprazole 30 mg twice daily, amoxicillin 750 mg twice daily and clarithromycin 200 mg twice daily, but repeat gastroscopy 3 mo after commencement of the initial treatment showed no regression or disappearance of the gastric hyperplastic polyposis. Histopathological examination of biopsy samples from the antrum and corpus showed persistent infection by the same organism and chronic active gastritis. The patient was subsequently treated with a 1-wk triple therapy consisting of rabeprazole 10 mg twice daily, amoxicillin 750 mg twice daily and metronidazole 250 mg twice daily[15]. Four weeks after cessation of the salvage treatment, the ^{13}C-urea breath test was negative. Three months later, repeat gastroscopy showed substantial decrease in size and number of the polyposis. A 2-year follow-up gastroscopy revealed almost complete regression of the lesions (Figure 2). *H pylori* infection was still negative (urea breath test) at the last follow-up, 3 years after commencement of the eradication treatment. However, the morphology of esophageal and colonic lesions remains unchanged.

DISCUSSION

Gastrointestinal involvement is common in CD[3-6]. Histopathologically different types of gastrointestinal polyps have been observed frequently in patients with CD[3-6]. In this regard, gastrointestinal hamartoma is considered as a criterion in the extensive set of formal criteria required for the diagnosis of CD proposed by International Cowden Consortium[14]. In one series of 51 individuals of whom 20 had a gastrointestinal workup, 16 had gastrointestinal lesions including 13 colonic polyps[16]. Typically, multiple polyps of the distal colon and rectum were seen with relative sparing of the proximal colon[16]. Multiple small polyps in the stomach and duodenum were also common[6,16]. Esophageal glycogenic acanthosis is a distinct lesion of affected patients with diffuse papillomatosis[3,17], as noted in our case. Gastroenterologists should consider the diagnosis of CD in any patient with such lesions in the digestive tract.

To date, there is little information on the association of *H pylori* infection with gastric manifestations of CD. Lee *et al* [18] reported the first case of CD with gastric hamartomatous polyposis accompanied by *H pylori*-related gastritis, albeit antibiotic treatment for the infection was not applied. In our patient, following cure of *H pylori* infection with salvage therapy, polyposis lesions significantly regressed, although polyposis had by no means regressed with unsuccessful first-line triple therapy. This relation provided further support for recent studies indicating a close relationship between hyperplastic polyp and persistent *H pylori* infection; cure of the infection results in regression or disappearance of most hyperplastic polyps[10,12,13].

One can speculate that the inflammatory cell infiltration and acceleration of epithelial cell turnover induced by *H pylori* infection contributes to the development and/or progression of hyperplastic polyps[10,11]. Most CD patients have been shown to carry germ line or somatic mutations of *PTEN* (*protein tyrosine phosphatase and tensin homolog*), which is a tumor suppressor gene located on chromosome 10q23[19,20]. This lipid phosphatase activity of *PTEN* products plays a role in the regulation of phosphoinositol 3-kinase and is relevant in limiting cell cycle progression and promoting apoptosis and thus suppressing cell cycle[2,4,19]. Therefore, in the formation of gastric hyperplastic polyps of CD, such *H pylori*-associated effect may facilitate the inherent tendency of cell proliferation and tissue disorganization predisposed by genetic alteration representative of *PTEN* mutation[2,4,19].

The risk that patients with hyperplastic polyps would develop gastric carcinoma was reported to be as high as 3.6%[21]. Hyperplastic polyps develop in atrophic mucosa in 40-75% of cases[22], and it is possible that in many cases of hyperplastic polyps, chronic atrophic gastritis, which is mostly the consequence of *H pylori* infection, increases the risk of developing gastric carcinoma[11,22,23]. In addition, the incidence of malignant transformation of gastric hyperplastic polyps is estimated at 1.5 to 3%[7]. In fact,

gastric carcinoma *in situ* among hyperplastic polyps has been described in a CD woman[24]. Therefore, we recommend anti-*H pylori* eradication treatment for patients with CD manifesting gastric hyperplastic polyps, when they present with concomitant *H pylori* infection.

Once the diagnosis of CD is made, affected patients have to be considered as high- risk patients for developing malignancies[2,5]. The most common associated malignancies are breast, thyroid and endometrial carcinomas[2,5]. A life-long follow-up is necessary for this CD woman. Colonic adenocarcinomas have been reported in patients with CD[25], albeit their association with this disease at molecular levels remains unclear. Therefore, the existing polyps should be addressed by repeat endoscopic surveillance in the present case.

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