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 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 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.

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**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[6]. 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[8,9]. Alimentary tract abnormalities found in CD primarily appear as multiple polyps of various histopathologic features including hamartomatous, hyperplastic, inflammatory, juvenile, lymphomatous and adenomatous polyps[10-16]. 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[9]. 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 polypl 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[15]. In addition, multiple, whitish, minute protrusions, which showed positive staining
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 subsequently 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 polypsis. 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 500 mg twice daily and metronidazole 250 mg twice daily [18]. Four weeks after cessation of the salvage treatment, the 13C-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 polyyps 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 polyyps of the distal colon and rectum were seen with relative sparing of the proximal colon [16]. Multiple small polyyps in the stomach and duodenum were also common [16-19]. 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 polyyp and persistent *H pylori* infection; cure of the infection results in regression or disappearance of most hyperplastic polyyps [10,11,13].

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 polyyps [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 polyyps 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 polyyps would develop gastric carcinoma was reported to be as high as 3.6% [20]. Hyperplastic polyyps develop in atrophic mucosa in 40-75% of cases [20], and it is possible that in many cases of hyperplastic polyyps, 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 polyyps is estimated at 1.5 to 3% [17]. In fact,
gastric carcinoma in situ among hyperplastic polyps has been described in a CD woman\textsuperscript{30}. Therefore, we recommend anti-\textit{H pylori} eradication treatment for patients with CD manifesting gastric hyperplastic polyps, when they present with concomitant \textit{H pylori} infection.

Once the diagnosis of CD is made, affected patients have to be considered as high-risk patients for developing malignancies\textsuperscript{25,26}. The most common associated malignancies are breast, thyroid and endometrial carcinomas\textsuperscript{22,23}. A life-long follow-up is necessary for this CD woman. Colonic adenocarcinomas have been reported in patients with CD\textsuperscript{23}, 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.

REFERENCES

1. Lloyd KM, Denis M. Cowden's disease: A possible new symptom complex with multiple system involvement. \textit{Ann Intern Med} 1963; 58: 136-142
2. Fishtarol SK, Anliker MD, Itin PH. Cowden disease or multiple hamartoma syndrome-cutaneous clue to internal malignancy. \textit{Eur J Dermatol} 2002; 12: 411-421
3. Kay PS, Soetikno RM, Mindelzun R, Young HS. Diffuse esophageal glycogenic acanthosis: an endoscopic marker of Cowden's disease. \textit{Am J Gastroenterol} 1997; 92: 1038-1040
4. Corredor J, Wambach J, Barnard J. Gastrointestinal polyps in children: advances in molecular genetics, diagnosis, and management. \textit{J Pediatr} 2001; 138: 621-628
5. Wirtzfeld DA, Petrelli NJ, Rodriguez-Bigas MA. Hamartomatous polyposis syndromes: molecular genetics, neoplastic risk, and surveillance recommendations. \textit{Ann Surg Oncol} 2001; 8: 319-327
6. Hizawa K, Iida M, Matsumoto T, K hogrogi N, Suekane H, Yao T, Fujishima M. Gastrointestinal manifestations of Cowden's disease. Report of four cases. \textit{J Clin Gastroenterol} 1994; 18: 13-18
7. Daibo M, Itabashi M, Hirota T. Malignant transformation of gastric hyperplastic polyps. \textit{Am J Gastroenterol} 1987; 82: 1016-1025
8. Neimark S, Rogers AI. Gastric polyps: a review. \textit{Am J Gastroenterol} 1982; 77: 585-587
9. Isomoto H, Inoue K, Furusuh H, Enjoji A, Fujimoto C, Yamakawa M, Hirakata Y, Omagari K, Mizuta Y, Murase K, Shimada S, Murata I, Kohno S. The role of endoscopy in the surveillance of premalignant condition of the upper gastrointestinal tract. Guidelines for clinical applications. \textit{Gastrointestinal Endosc} 1998; 34(Suppl 3): 18-20
10. Ohkusa T, Takashmizuh I, Fujiki K, Suzuki S, Shimoi K, Horiiuchi T, Sakurazawa T, Ariake K, Ishii K, Kumagai J, Tanizawa T. Disappearance of hyperplastic polyps in the stomach after eradication of \textit{Helicobacter pylori}. A randomized, clinical trial. \textit{Ann Intern Med} 1998; 129: 712-715
11. Oberhuber G, Stolte M. Gastric polyps: an update of their pathology and biological significance. \textit{Virchows Arch} 2000; 437: 581-590
12. Ljubicic N, Banic M, Kujundzic M, Antic Z, Vrklan M, Kovacevic I, Hrabar D, Doko M, Zovak M, Mihatov S. The effect of eradicating \textit{Helicobacter pylori} infection on the course of adenomatous and hyperplastic gastric polyps. \textit{Eur J Gastroenterol Hepatol} 1999; 11: 727-730
13. Mocck FW, Ward WW, Wolfson SE, Rumage WT, Wiemert TJ. Elimination of recurrent hyperplastic polyps by eradication of \textit{Helicobacter pylori}. \textit{Ann Intern Med} 1994; 120: 1007-1008
14. Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. \textit{J Med Genet} 2000; 37: 828-830
15. Isomoto H, Inoue K, Furusuh H, Enjoji A, Fujimoto C, Yamakawa M, Hirakata Y, Omagari K, Mizuta Y, Murase K, Shimada S, Murata I, Kohno S. High-dose rabeprazole-amoxicillin versus rabeprazole-amoxicillin-metronidazole as second-line treatment after failure of the Japanese standard regimen for \textit{Helicobacter pylori} infection. \textit{Aliment Pharmacol Ther} 2003; 18: 101-107
16. Starink TM, van der Veen JP, Arwert F, de Waal LP, de Lange GG, Gille J, Eriksson AW. The Cowden syndrome: a clinical and genetic study in 21 patients. \textit{Clin Genet} 1986; 29: 222-233
17. McGarry TJ, Wagner-Baker MJ, Ruggiero FM, Thiboutot DM, Hamep H, Zhou XP, Eng C. GI polyposis and glyco-genic anacanthosis of the esophagus associated with PTEN mutation positive Cowden syndrome in the absence of cutane-ous manifestations. \textit{Am J Gastroenterol} 2003; 98: 1429-1434
18. Lee HR, Moon YS, Yeom CH, Kim KW, Chun JY, Kim HK, Choi HS, Kim DK, Chung TS. Cowden’s disease—a report on the first case in Korea and literature review. \textit{J Korean Med Sci} 1997; 12: 570-575
19. Liaw D, Marsh DJ, Li J, Dahia PL, Wang SI, Zheng Z, Bose S, Call KM, Tsou HC, Peacocke M, Eng C, Parsons R. Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. \textit{Nat Genet} 1997; 16: 64-67
20. Chi SG, Kim HJ, Park BJ, Min HJ, Park JH, Kim YW, Dong SH, Kim BH, Lee JI, Chang YW, Chang R, Kim WK, Yang MH. Mutational abrogation of the PTEN/MMAC1 gene in gastrointestinal polyps in patients with Cowden disease. \textit{Gastroenterology} 1998; 115: 1084-1089
21. Stolte M, Bethke B, Sticht T, Burkhard U. Differentiation of focal foveolar hyperplasia from hyperplastic polyps in gastric biopsy material. \textit{Pathol Res Pract} 1995; 191: 1198-1202
22. Laxen F, Kekki M, Sipponen P, Siurala M. The gastric mucosa in stomachs with polyps: morphologic and dynamic evaluation. \textit{Scand J Gastroenterol} 1983; 18: 505-511
23. Veereman Wauters G, Ferrell L, Ostroff JW, Heyman MB. Hyperplastic gastric polyps associated with persistent \textit{Helicobacter pylori} infection and active gastritis. \textit{Am J Gastroenterol} 1990; 85: 1395-1397
24. Hamby LS, Lee EY, Schwarz RW. Parathyroid adenoma and gastric carcinoma as manifestations of Cowden's disease. \textit{Surgery} 1995; 118: 115-117
25. Carlson GJ, Nivatvongs S, Snover DC. Colorectal polyps in Cowden's disease (multiple hamartoma syndrome). \textit{Am J Surg Pathol} 1984; 8: 763-770

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