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Spontaneous Regression of Polyposis following Abdominal Colectomy and *Helicobacter pylori* Eradication for Cronkhite-Canada Syndrome

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Key Words

Cronkhite-Canada syndrome · Colonic carcinoma · Abdominal colectomy · *Helicobacter pylori* eradication · Spontaneous regression

Abstract

The etiology of Cronkhite-Canada syndrome (CCS) remains unknown and many cases are refractory to treatment. Therefore, new therapies are urgently needed. Furthermore, a number of CCS cases with gastrointestinal carcinoma have been reported. Our patient had rapid onset of CCS and early development of colon carcinoma associated with adenomas. High anterior resection of the sigmoid colon and ileostomy were performed, and her symptoms and endoscopic and histological findings improved. *Helicobacter pylori* eradication was carried out 2 years later, surgical closure of an ileal fistula the following year. After 4 months, upper gastrointestinal endoscopy and colonoscopy showed that the CCS lesions had completely disappeared, and biopsies confirmed a normal stomach, duodenum, ileum and colon histologically. The patient has maintained remission for 2 years. The clinical course of this case, showing complete regression of CCS lesions following abdominal colectomy and *H. pylori* eradication, suggests the significance of *H. pylori* infection in the treatment of CCS.

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Introduction

Cronkhite-Canada syndrome (CCS) was first described in 1955 by Cronkhite and Canada [1]. The main symptoms of CCS are diarrhea, weight loss, abdominal pain, and other gastrointestinal complications, such as protein-losing enteropathy and malnutrition with diffuse polyposis in the digestive tract. CCS is a rare non-genetic disease of unknown cause characterized by alopecia, atrophic fingernails, and skin hyperpigmentation. In the past, CCS was regarded clinically as a malignancy because of its poor prognosis, but recent advances such as high-calorie infusion and steroid therapy have achieved long-term survival in some cases. CCS was considered a benign condition, however, there are several case reports of CCS associated with gastrointestinal carcinoma [2–4] and, since the etiology of this syndrome remains unknown, many cases are refractory to treatment and there are still fatalities. Therefore, new therapies are urgently needed.

Our patient initially presented with diarrhea, and sessile polyposis was revealed in the colon, intestine and stomach by colonoscopy and upper gastrointestinal endoscopy. Colonic carcinoma was subsequently discovered in the sigmoid colon, necessitating sigmoidectomy and ileostomy. Subsequent amelioration of symptoms and regression of polyposis were achieved by the ileostomy. The patient also received *Helicobacter pylori* eradication therapy. After successful eradication of *H. pylori*, she underwent ileostomy closure and complete polyposis resolution has since been observed. We describe this rare case with complete regression of CCS lesions and consider novel treatments for CCS.

Case Report

A 52-year-old woman, previously in good health without symptoms, developed diarrhea with lower abdominal pain during bowel movements and hematochezia, which continued for more than 2 weeks, after ingesting oysters and goat meat. At our hospital, colonoscopy demonstrated diffuse edema and a markedly erythematous elevated lesion from the end of the ileum to the rectum (fig. 1a). After hospitalization, infectious enteritis was suspected, but stool culture showed no obvious pathogens and there were no parasites in stool specimens. Upper gastrointestinal endoscopy showed salmon roe-like multiple elevated lesions with marked erythema involving almost the entire stomach (fig. 2a) and there was edematous mucosa in the antrum (fig. 2b), similar to that in the colon, as well as similar mild polypoid lesions in the duodenum. Initial pathological findings showed non-specific chronic inflammatory cell infiltration, edema and thickening of the colonic mucosa and crypts with cystic dilatation in the intestine (fig. 3a). However, neither foveolar gland hyperplasia nor interstitial inflammatory cell infiltration was found in the stomach.

Her symptoms persisted after starting 5-ASA and she also showed alopecia and glossitis 1 month later. At the second colonoscopy, an elevated tumor 30 × 35 mm was observed in the sigmoid colon (fig. 1b). Since the biopsy specimen was consistent with group 5, a well-differentiated adenocarcinoma, high anterior resection of the sigmoid colon and ileostomy were performed. She was initially managed with anti-flatulence and anti-diarrhea medications. Even when these treatments were stopped, the diarrhea, alopecia and glossitis continued to gradually improve. Pathological examination revealed well-differentiated adenocarcinoma with an adenoma component in the colon. Detailed examination of the surrounding mucosa revealed cystic dilatation of glands and edema, infiltration of eosinophils with plasma cells and lymphocytes, and spread of lymphangitis. CCS associated with sigmoid colon cancer (0–1, pM N0 M0) with tubular adenoma was thus diagnosed (fig. 3b). Colonoscopic

observation via the ileostomy, after surgery, revealed amelioration of the edema and erythema in the ileum, ileocecal region and ascending colon.

On colonoscopy 6 months later, the findings in the ileum had almost disappeared and erythematous polypoid lesions and edematous mucosa showed regression in the colon. Furthermore, the similar lesions initially detected in the gastroduodenum were no longer apparent. Although spread of cystic crypts was observed in some portions of the intestine, colonic histology, i.e. mucosal thickening, showed improvement 1 year later. Gastric foveolar hyperplasia and edema disappeared, and mucosal thickness was normal in the stomach. On the other hand, on colonoscopy 2 years later, while polyps were no longer visible, erythema and petechiae persisted, reflecting diversion colitis (fig. 1c). The thickness of the colonic mucosa was histologically normal with no edema, but extended cystic crypts remained in portions of the intestine. Upper gastrointestinal endoscopy confirmed the absence of gastric polyps or other abnormal findings in the duodenum (fig. 2c). Histopathological features of the stomach indicated normal thickness without mucosal edema, and chronic gastritis with positive *H. pylori* histology and serology.

Subsequently, *H. pylori* eradication was carried out using amoxicillin and clarithromycin. The ^{13}C urea breath test result was negative, indicating successful treatment. After 4 months, the endoscopic and histological findings of gastritis had also improved and active inflammation had disappeared (fig. 2d). On further observation the following year, colonoscopy showed diversion colitis, but no CCS findings. Surgical closure of an ileal fistula was carried out and, after 4 months, upper gastrointestinal endoscopy and colonoscopy showed that not only the CCS lesions but also the diversion colitis findings had completely disappeared. Histological biopsies confirmed a normal stomach, duodenum, ileum and colon. As the patient remained asymptomatic during observation, she has since been followed at our outpatient clinic without medication. After 2 further years, colonoscopy and upper gastrointestinal endoscopy showed normal findings (fig. 1d). Histological examination showed no CCS lesions and no diversion colitis findings (fig. 3c).

Discussion

The number of CCS cases in Asia, including Japan, is reportedly high. Although CCS has been recognized as a benign non-genetic disease, it manifests clinically as protein-losing gastroenteropathy, and relapse or exacerbation is common despite temporary improvements with medical therapy, such as steroids. CCS was formerly considered to have a poor prognosis and a high mortality rate due to the complication of carcinoma, and many patients present with malignancy. Although the characteristics of CCS polyps are considered to be non-neoplastic in nature, a relatively high frequency of gastrointestinal carcinoma in CCS patients has been reported [2–5]. The course in our case was also complicated by early-onset carcinoma necessitating partial resection of the sigmoid colon and ileostomy. Subsequently, symptoms and endoscopic and histological findings showed amelioration, and the patient was followed without further intervention. She underwent *H. pylori* eradication 2 years after surgery and the ileostomy was closed the following year, after *H. pylori* eradication. Three months after this closure, CCS lesions of the colon and stomach were no longer visible macroscopically or histologically. She remained in this remission state for 1 year thereafter.

To our knowledge, there are no prior reports of CCS cases such as our present patient undergoing surgical treatment and eradication of *H. pylori*. This treatment strategy resulted in remission without steroid administration. Steroids have commonly been administered for

CCS and cases achieving temporary improvement or even long-term remission have been reported [6]. However, there were numerous recurrences and effectiveness, as compared to other treatments, has not been established. Among reports supporting surgical treatment of CCS, there are descriptions of operations for complicated carcinomas. The patients showed improvement of hypoproteinemia and reduced protein leakage postoperatively. Therapeutic effects would presumably have been obtained if the site in the digestive tract, harboring polyposis and causing protein leakage, had been resected along with the carcinoma. Daniel et al. [7] reported in their literature review that symptomatic remissions were observed in 2 of 6 cases who underwent subtotal gastrectomy alone. In addition, symptomatic remissions were attributed to the operations alone in 3 of 7 patients receiving large bowel resection, among 55 CCS cases. In our case, only partial resection of the sigmoid colon was performed for tumor removal from the sigmoid colon and polyposis remained at other sites. Simultaneous ileostomy of the terminal ileum resulted in subsequent regression of polyposis. Therefore, it is possible that changes in bacterial dynamics within the intestinal flora are related to the improvement achieved by ileostomy in our patient.

Furthermore, clear evidence implicating *H. pylori* infection in the pathogenesis of CCS is lacking. Okamoto et al. [8] and Kim et al. [9] recently reported that lesions such as diffuse polyposis showed progressive remission after *H. pylori* eradication using antibiotics in patients with CCS. *H. pylori* usually inhabits the gastric mucosa, but this microorganism has reportedly been cultured from stool specimens of *H. pylori* carriers. *H. pylori* might injure the intestinal mucosa when passing through the intestinal tract, and/or activation of lymphocytes in the gastric mucosa by *H. pylori* may induce an immune response against this microorganism in the intestinal mucosa [10]. As with MALToma of the stomach, colonic MALToma reportedly improves in response to *H. pylori* eradication [11]. Based on these reports and our evidence, we cannot rule out the possibility that *H. pylori* infection is involved in the development or exacerbation of CCS polyps, but the underlying mechanism remains uncertain. Accumulation of such cases and further research are necessary to explain the pathogenesis of CCS and to devise novel treatments for this disease.

Disclosure Statement

The authors declare that they have no conflict of interest.

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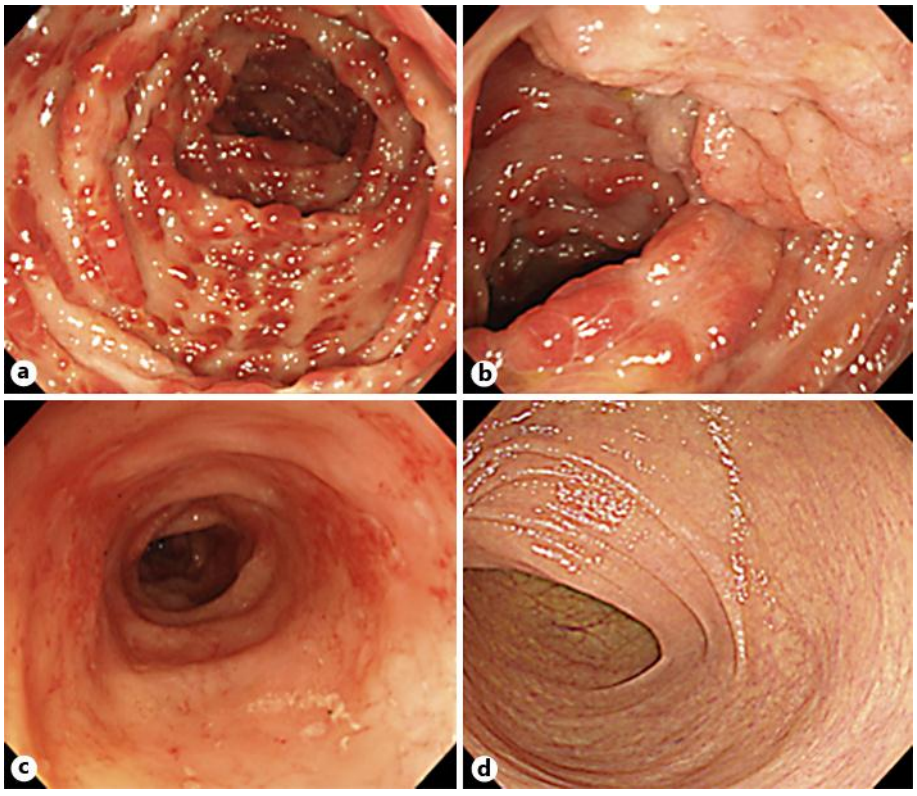

Fig. 1. **a** Diffuse edema and a markedly erythematous elevated lesion extending from the end of the ileum to the rectum. **b** Diffusely edematous and markedly erythematous elevated lesions involved the entire colon and an elevated tumor, 30 × 35 mm, in the sigmoid colon were detected. **c** Polyps were no longer visible, though erythema and petechiae persisted, reflecting diversion colitis. **d** Five years after the operation and three years after *H. pylori* eradication, the CCS lesion had completely disappeared from the colon.

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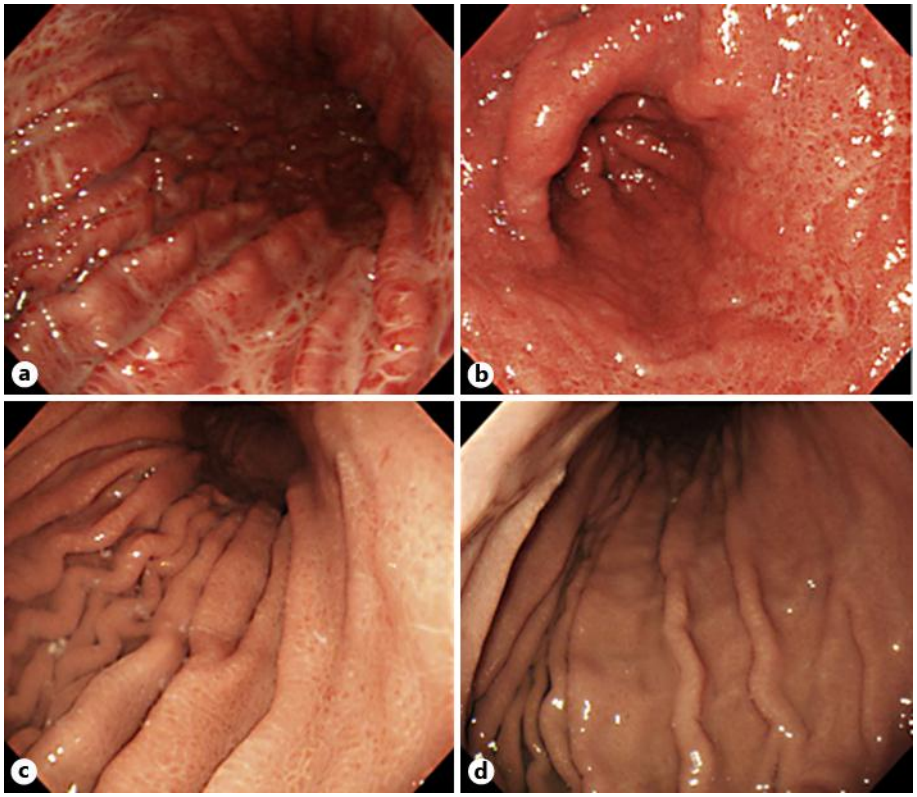

Fig. 2. Salmon roe-like multiple elevated lesions with marked erythema involving almost the entire stomach (**a**) and edematous mucosa in the antrum (**b**) are shown. **c** Upper gastrointestinal endoscopy confirmed the absence of gastric polyps. **d** Four months after *H. pylori* eradication, the endoscopically demonstrated gastritis had improved and active inflammation had disappeared.

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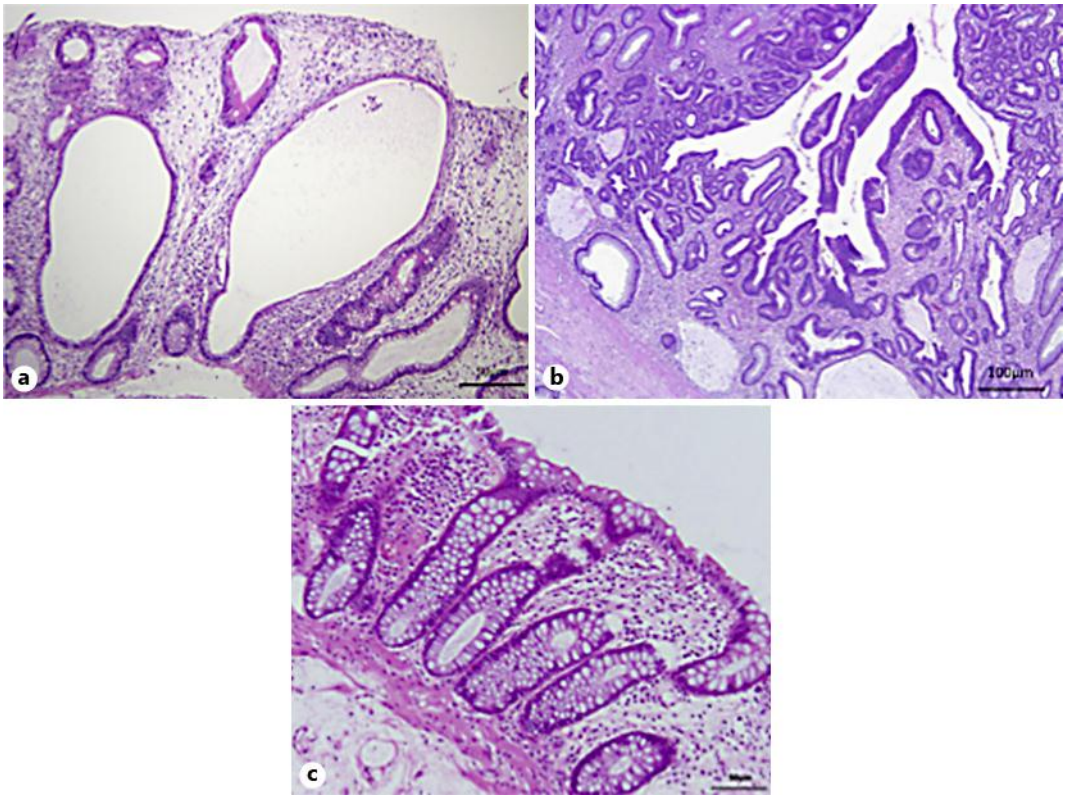

Fig. 3. **a** Initial pathological findings included edema and thickening of the colonic mucosa and crypts with cystic dilatation in the colon. **b** Histological examination revealed cystic dilatation of glands and edema, associated with well-differentiated adenocarcinoma and tubular adenoma in the sigmoid colon. **c** Five years after the initial operation, histological examination showed that not only the CCS lesions but also the diversion colitis findings had completely disappeared (H&E staining).