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CASE REPORT

# Cronkhite–Canada syndrome tends to be accompanied by colorectal cancer: Report of seven cases

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## Abstract

Cronkhite–Canada syndrome (CCS) can be difficult to diagnose. To diagnose CCS, it is important to perform endoscopic examination for patients with chronic diarrhea, check for the presence or absence of polyposis, and evaluate inflammation in the mucosa between the polyps. This study reported seven cases of CCS. The age of the patients, which included four men and three women, ranged 48–72 years, and all patients were Asian. The most common symptom among these patients was chronic diarrhea. Three of the patients had rectal cancer. In two patients, the lesions were detected at an early stage and resected via endoscopic treatment. CCS is associated with a high risk of malignant gastrointestinal lesions, especially rectal cancers, and periodic surveillance endoscopy and careful observation are required.

## Introduction

Cronkhite–Canada syndrome (CCS) is a rare non-hereditary disease characterized by multiple non-neoplastic polyps in the gastrointestinal tract. Approximately 500 cases have been reported globally.[1] The main symptoms are dysgeusia, chronic diarrhea, and dermatological manifestations such as alopecia, onychodystrophy, and hyperpigmentation.[1]

If a patient exhibits these typical symptoms, the diagnosis of CCS is not difficult. However, CCS is often difficult to diagnose in patients who do not exhibit these symptoms during the initial disease stage.[2–4] Notably, because endoscopic findings can contribute to the diagnosis of CCS, recognition of these findings is important for an accurate diagnosis. Additionally, CCS is reportedly accompanied by life-threatening malignant neoplasms, especially in the colorectum.[1] There are few coherent reports on colorectal cancer as a comorbidity of CCS. In this study, we reported the clinicopathological and endoscopic features of seven patients with CCS, including some patients with coincident colorectal cancer, at our hospital.

## Case report

This retrospective study included seven patients diagnosed with CCS at the Japanese Red Cross Wakayama Medical Center between 2003 and 2020. CCS was defined as the presence of multiple polyps and at least one of the following main symptoms: dysgeusia, chronic diarrhea, and dermatological manifestations such as alopecia, onychodystrophy, or hyperpigmentation. The clinical characteristics and endoscopic findings (such as the distribution and characteristics of polyps and the presence or absence of mucosal inflammation between polyps) of the patients were evaluated. Moreover, the endoscopic characteristics of coincident colorectal cancers were reviewed.

Table 1 presents the patients' clinical characteristics and outcomes. Approximately half of the patients presented with dysgeusia, chronic diarrhea, and dermatological manifestations at the first visit. Chronic diarrhea occurred in five patients. Remission was achieved in all six patients treated with prednisolone. The endoscopic findings are also presented in Table 1. Polyposis in the colon was observed in all patients, and polyposis in both the stomach and colon was observed in six patients. The

**Table 1** Clinical characteristics, outcomes, and endoscopic findings

| | | *N* = 7 |
|---|---|---|
| Clinical characteristics and outcomes | | |
| Age | Median(range) | 56 (48–72) |
| Gender | Male: Female | 4: 3 |
| Symptoms at initial visit | | |
| Chronic diarrhea | | 71% (5/7) |
| Dysgeusia | | 57% (4/7) |
| Dermatological manifestation[†] | | 43% (3/7) |
| Treatment | | |
| Prednisolone | | 86% (6/7) |
| Eradication of HP[‡] | | 43% (3/7) |
| Follow-up period (months) | Median (range) | 24 (0–72) |
| Therapeutic outcome | Remission | 100% (6/6)[§] |
| Long term outcome | Survival rate | 86% (6/7)[¶] |
| Endoscopic findings | | |
| Polyposis | Stomach | 86% (6/7) |
| | Colon | 100% (7/7) |
| Endoscopic findings of polyps[††] | | |
| Distribution | Confluent: Sparse | 5: 1 |
| Color | Reddish | 100% (6/6) |
| Inflammation[‡‡] in the mucosa between the polyps | | 83% (5/6) |
| Associated with malignant tumor | | 50% (3/6)[§§] |

[†]Alopecia, onychodystrophy, or hyperpigmentation.
[‡]*Helicobacter pylori*.
[§]One patient moved to another prefecture.
[¶]One patient died of lung cancer.
[††]One patient could not be evaluated.
[‡‡]Low vascular permeability or edema.
[§§]All three cases were rectal cancers.

distribution of polyps was confluent in five patients and sparse in one patient. All polyps were reddish. Inflammation in the mucosa between the polyps was observed in five patients. Three patients were diagnosed with rectal cancer during the observation period. The macroscopic type of all three cancers was 0-Is,[5] and the tumor size ranged 15–30 mm. Two cancers were detected at an early stage and resected completely via endoscopic treatment.

Regarding the three patients with rectal cancer, Case 1 was a man in his 70s who was admitted to our department because of epigastric pain, diarrhea, dysgeusia, and dermatological manifestations. He was diagnosed with CCS based on his endoscopic findings, and he was treated with prednisolone. Remission was achieved after 1 month of treatment. The cancer was not present at the time of diagnosis as determined by colonoscopy. Repeat colonoscopy was performed 1 year after the initial colonoscopy. Two years after achieving remission, a 4-cm protruded lesion was detected in the rectum (Fig. 1a,b). The lesion was resected via endoscopic mucosal resection (EMR). The pathological result was well-differentiated adenocarcinoma, pTis, ly0, v0, HM0, VM0 (Fig. 1a,b). Case 2 was a woman in her 60s who visited her local doctor because of weight loss. She had pigmentation on both hands, and she subsequently developed dysgeusia. The patient was admitted to our hospital. CCS was suspected on the basis of the endoscopic findings. A protruded lesion was detected in the rectum, and it was suspicious for an epithelial neoplasm. EMR was performed. The pathological result was well-differentiated adenocarcinoma, pTis, ly0, v0, HM0, VM0. We considered the lesion to be a sporadic cancer occurring separately from the development of the hamartomatous lesion because the entire tumor was adenocarcinoma. Case 3 was a 70-year-old woman who visited our hospital for diarrhea. Upper gastrointestinal endoscopy revealed multiple polyps in the stomach, and CCS was suspected. Colonoscopy revealed multiple polyposis and type 2 advanced cancer in the rectum, and she underwent surgical resection. The pathological result was adenocarcinoma, tub1, pSS, INFb, int., ly1, v1, pPM0, pDM0, pRM0, pN0, Stage 2, Cur A. The patient was treated with prednisolone after surgery, which led to disappearance of the polyps, and no recurrence was detected by endoscopic examinations for 8 years.

## Discussion

Cronkhite and Canada first described CCS in 1955.[3] It is a rare non-hereditary disease, and approximately 500 cases have been reported worldwide.[1] Additionally, 75% of all CCS cases reported in the global literature occurred in Japan.[6] The disease has a male predominance (male: female ratio of 3:2),[7] and the mean age at onset is 63.5 years (range, 31–86).[1] The sex and age at onset in our study were similar to these previous results.

CCS is characterized by gastrointestinal polyposis, dermatological manifestations (alopecia, onychodystrophy, and hyperpigmentation), and dysgeusia.[1] The diagnosis of CCS is straightforward if characteristic dermatological manifestations and dysgeusia are present from the initial stage of the disease; however, because these symptoms are frequently absent in the initial stage, the diagnosis is often difficult.[1] According to previous reports, <50% of patients with CCS have dysgeusia or dermatological manifestations,[1,8] in line with our findings that three patients presented with typical dermatological manifestations and four presented with dysgeusia. Because chronic diarrhea is considered the most frequent initial manifestation of CCS, it is important to recommend endoscopic examination for patients with chronic diarrhea to identify CCS in the initial stage.

The typical endoscopic findings of CCS include polyps characterized by severe edema.[1,3,4] Polyposis of the colon was observed in all patients in our study. Moreover, inflammation in the mucosa between the polyps, another typical finding of CCS, was observed in five patients. The differential diagnoses of CCS include familial adenomatous polyposis, Cowden syndrome, and Peutz–Jeghers syndrome.[7] Inflammation in the mucosa between the polyps differs from the endoscopic findings of the other polyposis syndromes.[1,3,4] When polyposis is found in the stomach or colon, the mucosal inflammation and polyp distribution should be evaluated to distinguish CCS from other polyposis syndromes. Therefore, it is important to assess the presence or absence of polyposis and evaluate inflammation in the mucosa between the polyps.

The prognosis of CCS is poor. Its 5-year mortality rate is 55%, and most deaths are associated with malnutrition, hypoalbuminemia, repetitive infection, sepsis, heart failure, and gastrointestinal bleeding.[7] However, the prognosis of CCS appears to be substantially improved by the combination of prednisolone

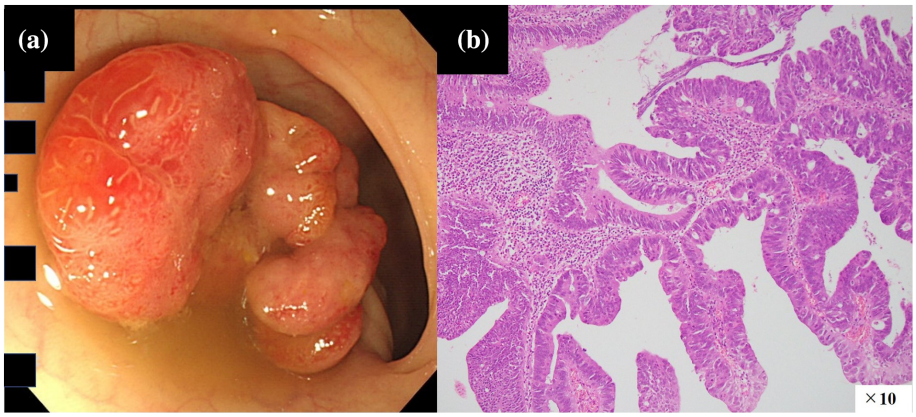


**Figure 1** (a, b) Two years after achieving remission, a 4-cm protruded lesion was detected in the rectum. The lesion was subjected to hematoxylin–eosin staining (×10 magnification). The pathological result was well-differentiated adenocarcinoma.

therapy, nutritional support, and periodic endoscopic surveillance.[1] Conversely, patients with CCS might have cancers of the gastrointestinal tract and other organs.[1] If gastrointestinal cancer is detected at an early stage, it can be resected endoscopically; thus, periodic endoscopic surveillance is important. Three patients in our study had rectal cancer. Rectal cancer occurred in three of six patients (50%) over a relatively short median follow-up period of 24 months after the onset of CCS. One patient had advanced cancer, whereas the other two had early cancer that could be treated endoscopically. In Case 1, rectal cancer was detected 2 years after the remission of CCS. It was possible that the cancer occurred after remission or that the cancer became apparent because of the improvement of mucosal inflammation. Even if the remission of CCS could be achieved and the patient's symptoms improve, follow-up via colonoscopy shortly after confirming remission could lead to the early detection of coexisting colorectal cancer. In Case 2, rectal cancer was detected at the time of diagnosis. Colorectal cancer could already be present in a colon with strong mucosal inflammation and polyposis. Thus, when CCS is suspected, it is necessary to carefully investigate the presence or absence of gastrointestinal cancer, especially rectal cancer.

In conclusion, to accurately diagnose CCS, it is important to recommend endoscopic examination for patients with chronic diarrhea and confirm the presence or absence of polyposis and inflammation in the mucosa between the polyps. Moreover, CCS is associated with a high risk of gastrointestinal malignant lesions, especially rectal cancer, and periodic surveillance endoscopy and careful observation are required.

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## Ethics approval

This study was approved by Institutional Reviewer Board of Japanese Red Cross Wakayama Medical Center (Registry No: 1109).

## Patient consent

Informed consent was obtained from the patients for the conduct of this study and its subsequent publication.

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