



Clinical and Radiological Features of Cronkhite–Canada Syndrome: A Case Report

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Abstract

Keywords

- ▶ Cronkhite–Canada syndrome
- ▶ intestinal polyps
- ▶ hyperpigmentation
- ▶ malabsorption
- ▶ protein-losing enteropathy

Cronkhite–Canada syndrome is a rare non-hereditary disease characterized by gastrointestinal hamartomatous polyposis and protein-losing enteropathy. The presenting symptoms are onychodystrophy, skin pigmentation, alopecia, weight loss, and diarrhea. Diagnosis is suggested by a combination of clinical, imaging, and endoscopy findings, and histology is necessary for confirmation. Here we describe a case of a 54-year-old man presenting with watery diarrhea, colicky abdominal pain, nasal obstruction, and weight loss for 6 months. Endoscopy showed multiple polyps in the stomach, duodenum, and colon. These were seen on computed tomography (CT) enterography along with polyps in the small bowel. A final diagnosis was made after the biopsy.

Introduction

Cronkhite–Canada syndrome (CCS) is a rare systemic non-hereditary disease characterized by gastrointestinal (GI) hamartomatous polyposis, ectodermal changes including onychodystrophy, skin pigmentation, and alopecia, weight loss, and diarrhea.¹ CCS typically manifests in the fifth and sixth decades and is more common in males, with a ratio of 3:2.² It is associated with high mortality due to complications such as malnutrition, protein-losing enteropathy, gastrointestinal bleeding, and infection.³

The pathogenesis of CCS is not fully understood; an autoimmune etiology is proposed.⁴ There is a rare association of CCS with gastrointestinal cancers, including gastric

cancer and colorectal cancer.^{4,5} A diagnosis of CCS can be suggested based on the combination of clinical presentation, imaging features, and findings on endoscopy.⁶ Histology is however required in most cases to confirm the disease.

The radiological investigations that assist in the diagnosis include barium studies such as barium upper gastrointestinal study, barium enema, and computed tomography (CT) and/or magnetic resonance (MR) enterography. They also help in the detection of associated pathologies and complications and exclude other diseases with similar clinical presentations. There are sporadic reports discussing the imaging features of CCS.⁷ In this report, we describe the imaging features of a diagnosed case of CCS along with clinical and endoscopic findings.

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Fig. 1 Physical examination findings of CCS show (A) hyperpigmentation of the skin, dark brown macular lesions on cheeks and forehead, and hair loss on the scalp, eyebrows, and eyelashes. (B) Skin hyperpigmentation on the dorsum of the hand, subungual hyperkeratosis with distal onycholysis, and loss of fingernails. (C) Nail dystrophy, onycholysis, and onychomadesis in the feet.

Case Report

A 54-year-old male presented to the gastroenterology clinic of our institute with a history of watery diarrhea, colicky abdominal pain, and weight loss of 5 kg in the past 6 months. The stool frequency was 10 to 15 times/day and was not associated with blood, fat, or oil. Further, there was a history of thickening of nails in all four limbs, scalp hair loss, and darkening of skin for 4 months. There was no history of fever, cough, or shortness of breath. There was a history of endoscopic nasal surgery for nasal polyposis 1 year ago. The family history was unremarkable.

Clinical examination revealed hair loss on the scalp, eyebrows, eyelashes, and limbs with associated onychodystrophy, onycholysis, and onychomadesis (proximal separation of the nail plate from the nail matrix due to a temporary cessation of nail growth). In the present case, most of the finger and toe nail changes started with proximal separation (► Fig. 1). Laboratory investigations revealed hypoalbuminemia (2.5 mg/dL), hypoproteinemia (4.6 g/dL), mild leukocytosis (16,520 cells/mm³) with neutrophilia (82.9%), hemoglobin of 11.7 g/dL, hematocrit of 35.4%, hypocalcemia (7.3 mg/dL), and normal serum phos-

phate (3.2 mg/dL). The 24-hour urinary calcium (25 mg/day) and phosphate (775 mg/day) were low. His liver function tests and triple-phase technetium^{99m} methylene di-phosphonate bone scan were normal. No abnormal radiotracer activity was seen in the blood pool phase and 3 h and 5 h delayed phases.

Barium study revealed multiple filling defects in the stomach (► Fig. 2A), duodenum, and small bowel. Multiple tiny projections (called *whiskering* due to barium trapped between the small, nodular excrescences of enlarged rugae) were also seen along the greater curvature of the stomach and antrum with thick gastric folds (► Fig. 2A). CT enterography showed diffuse nodular mucosal thickening of the stomach and duodenum with a large polyp in the first part of the duodenum (► Fig. 2B). Nodular mucosal thickening and multiple small polyps were also seen in the ileum, ileocecal junction (► Fig. 2C), colon, and rectum (► Fig. 2D). All polyps showed homogenous enhancement similar to the mucosa and most of them were sessile in appearance.

Upper gastrointestinal endoscopy revealed diffuse polyposis in the stomach and duodenum (► Fig. 3) Colonoscopy



Fig. 2 (A) Barium study shows prominent, thickened, and irregular rugal folds with filling defects and the characteristic whiskering along the greater curvature of the stomach (arrows). (B) Coronal CT enterography image shows the thickened wall of the stomach with a large homogeneously enhancing polyp in the first part of the duodenum (arrow). Small bowel loops show mild diffuse thickening of the mucosal folds. (C) Coronal CT enterography image shows large homogeneously enhancing polyp at the ileocecal junction (arrow). (D) Sagittal CT enterography image shows mucosal thickening with multiple polyps in the rectum (arrow).

showed edematous mucosa of visualized ileum and cecum with multiple sessile polyps in the ileocecal junction (→**Fig. 3B**), colon, and rectum. The frequency of polyps increased from rectum to cecum. Biopsies obtained from the polyps of the stomach, colon, and rectum showed dilated oxyntic glands with markedly irregular foveolar glands and surface villiform changes (→**Fig. 4**). The colonic polyps showed cystically dilated irregular crypts with flattened epithelium, luminal mucin pool, and focal micro-papillary proliferation of epithelial lining. The polyp stroma was edematous and showed scattered mononuclear cells and eosinophils, suggestive of hamartomatous polyps (→**Fig. 4D**).

A final diagnosis of Cronkhite Canada Syndrome was established and the treatment was initiated with steroids. After 6 months of follow-up, the patient's symptoms resolved and he is doing well.

Discussion

Cronkhite Canada syndrome is a rare non-hereditary disease, characterized by gastrointestinal hamartomatous polyposis and protein-losing enteropathy.¹ More than 75% of the reported cases are from Japan. The polyps mostly occur in the stomach and colon but can occur anywhere in the GI tract except the esophagus.⁶ Small sessile polyps are more commonly seen than pedunculated ones.⁸ Typically, there is thickening of the gastric rugal folds with polyps carpeting the mucosa. Microscopically, the involved tissue is edematous and inflamed.^{8,9}

The etiology of CCS is suspected to be autoimmune in origin and until now no strong evidence of genetic predisposition has been found. Elevated serum levels of IgG4 and ANA (antinuclear antibody) with increased IgG4 mononuclear cell staining are shown to be associated with CCS.^{10,11} An

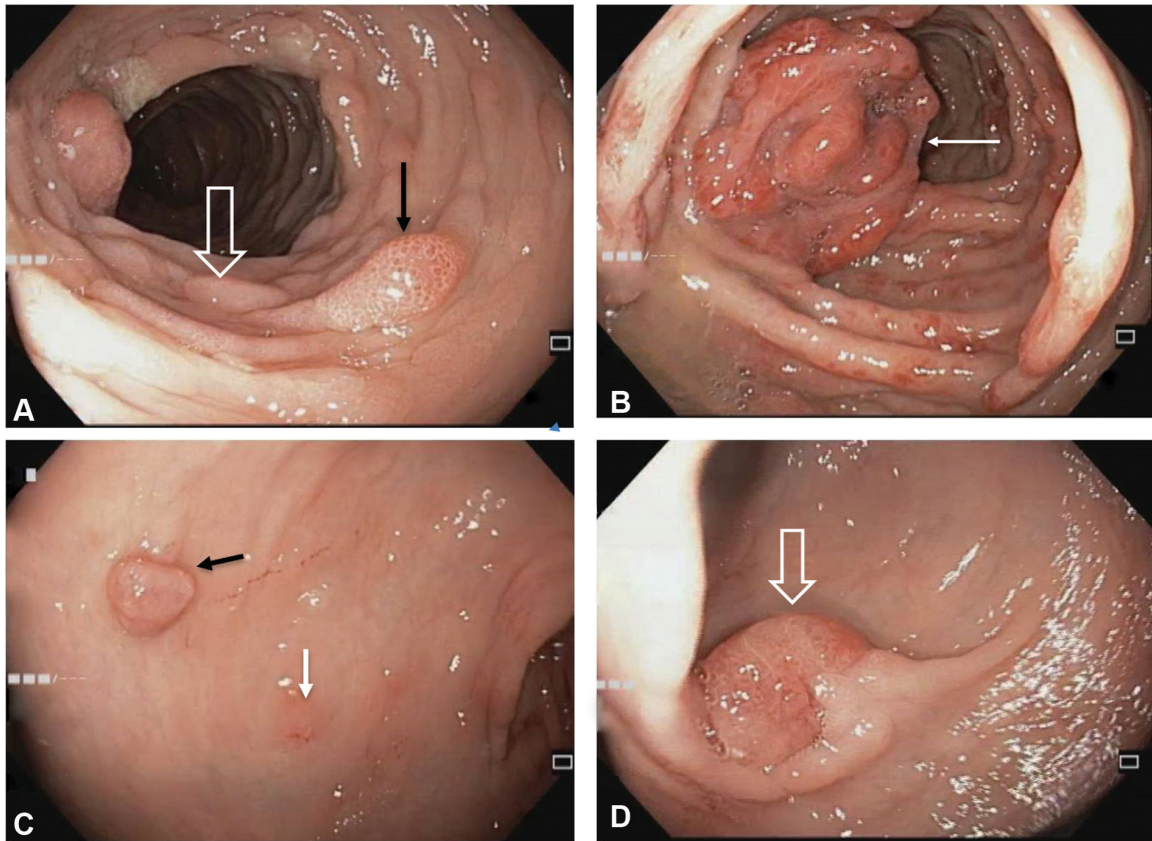


Fig. 3 Endoscopy shows (A) edematous mucosa (open arrow) and sessile polyp (solid arrow) in the ascending colon; (B) a large polyp in the ileocecal junction (arrow); (C) mucosal edema (white arrow) with a polyp (black arrow) in the stomach and; (D) polyp in the first part of the duodenum (open arrow).

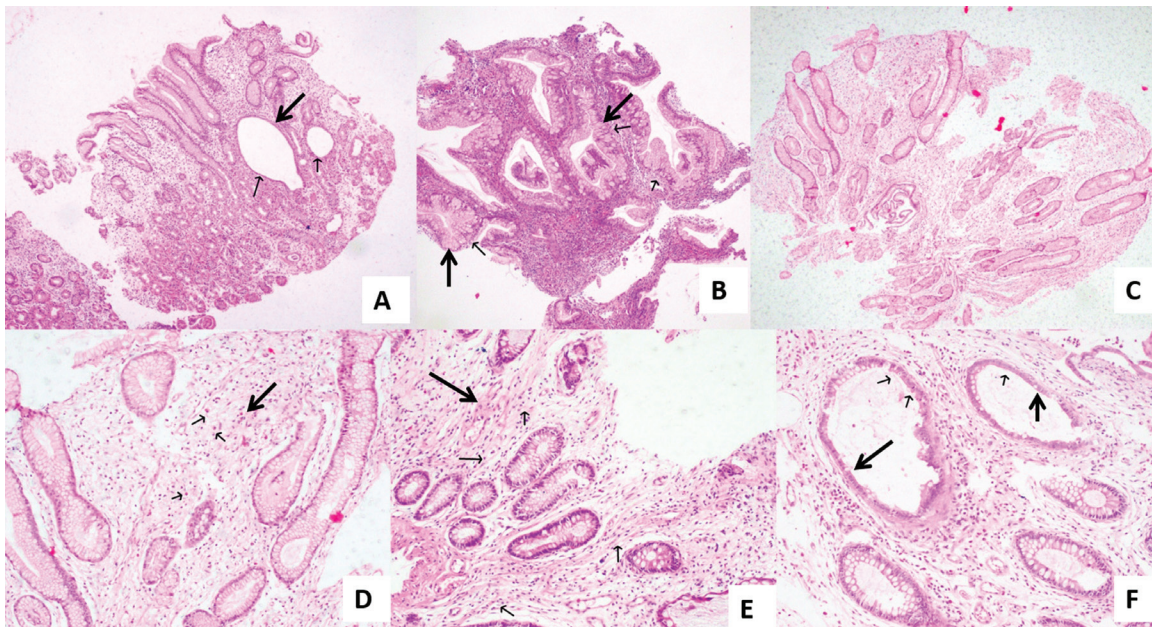


Fig. 4 (A–F) Sections examined from multiple polypectomies show focal features of fundic gland polyp with dilated oxyntic glands (arrows) [A x20], hyperplastic gastric polyp with markedly irregular foveolar glands (arrows) with surface villiform changes [B x40], a sessile gastric polyp with edematous mildly inflamed stroma and irregular branching foveola [C x20]. The polyp stroma is edematous and shows scattered mononuclear cells and eosinophils (arrows) [D x100]. A sessile colonic polyp showing similarly edematous stroma with mononuclear cell infiltrate including eosinophils and splaying of thin collagen and muscle fibers (arrows) [E x 100]. The colonic polyps show cystically dilated irregular crypts with flattened epithelium (arrows), luminal mucin pool, and focal micropapillary proliferation of epithelial lining [F x200].

Table 1 Table differentiating CCS from other common polyposis syndromes^{9,21}

Features	Cronkhite–Canada syndrome	Peutz–Jeghers syndrome	Juvenile polyposis	Familial adenomatous polyposis
Polyp type	Hamartomatous polyp	Hamartomatous polyp	Hamartomatous	Adenomatous (dysplasia)
Inheritance	Acquired/autoimmune	Hereditary-AD, <i>STK 11</i> gene mutation	AD in 25% of cases- <i>SMAD4</i> and <i>BMPRTA</i> gene mutation	Hereditary-AD, <i>APC</i> gene
Age group	Middle age (50–60 years)	Less than 30 years	Childhood (average 10 years)	Childhood and adolescents (average 16 years)
Clinical features	Diarrhea, malnutrition, abdominal pain, protein-losing enteropathy, alopecia, loss of nails, brown macules on hands and feet	Brown black macules on lips and buccal mucosa, abdominal pain (intussusception)	Bowel obstruction/intussusception, protein-losing enteropathy, repeated bronchopulmonary infections	Rectal bleeding, diarrhea, anemia, congenital hypertrophy of retinal pigmented epithelium (CHRPE), osteomas, desmoid tumors, other organ tumors
Histological features	Benign features, inflammatory cells with eosinophils, submucosal edema, mostly located in the lamina propria, hyperplasia of the foveolar epithelium, focal hyperplasia, and cystic dilation of the mucosal glands	Polyp shows smooth muscle core, displacement of epithelial elements into the submucosa, muscularis propria, and subserosa	Little or no smooth muscle core, expanded, edematous and inflamed lamina propria, cystically dilated glands. Intervening mucosa is not inflamed	Tubular, villous or tubulovillous adenomas with dysplasia, fundic gland polyps usually seen
Risk of malignancy	Very low	2–20% risk with coexisting adenoma	3–5% may turn into adenoma and increase the risk of malignancy	High, almost all carriers develop colorectal cancer by 35–40 years of age.
Radiological Features	Carpet tracking of multiple sessile polyps in stomach > small intestine > colon. Gastric rugal fold thickening. (characteristic whiskering on barium)	Jejunum, ileum > duodenum > colon and stomach involvement, sessile or pedunculated polyps occur in clusters	Small bowel and colon involved >stomach, Dilated bowel loops due to obstruction/intussusception	Innumerable small polyps (<5 mm), features of colorectal carcinoma may be seen such as ulceration and narrowing of bowel lumen and lymph nodes, and metastasis

Abbreviations: AD, autosomal dominant; CCS, Cronkhite–Canada syndrome.

association between CCS and hypothyroidism and other autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, and scleroderma has been reported.¹² Mental and physical stress have also been reported as contributory factors.¹³

The most common initial symptom of CCS is diarrhea along with symptoms related to malabsorption including weight loss, anemia, edema, dysgeusia, and anorexia.⁹ Paresthesias, seizures, and tetany, because of electrolyte abnormalities, have also been reported. Ectodermal abnormalities associated with the disease include nail dystrophy, thinning, splitting, and shedding from the nailbeds, and alopecia of the scalp and body hair.¹² The extremities, palms, soles, face, and neck show dark brown macules and hyperpigmentation of the skin. Death in CCS results from GI bleeding, sepsis, and heart failure. The 5-year survival rate is around 55%.¹⁴

Radiological investigations include CT or MR enterography and barium studies that aid in making a diagnosis and differentiate it from other bowel diseases presenting with similar symptoms.⁶ The radiologist may be the first to suggest a diagnosis in cases where there are mild symptoms or delayed skin changes. In our case, the patient was symptomatic with skin changes which pointed toward a diagnosis of CCS. The radiological appearance of CCS on barium studies includes thickened rugal folds with characteristic “whiskering” (i.e., barium trapped between the interstices of small polyps or barium trapped between the hypertrophied rugae (sulci gastricae) in the stomach, especially along the greater curvature.¹⁵ Whiskering can also be seen in Menetrier’s disease, lymphoma, and other generalized polyposis syndromes such as Peutz–Jeghers syndrome. But this appearance is more commonly seen in CCS due to the innumerable polyps carpeting the stomach.¹⁵ Polyps in the Peutz–Jeghers syndrome occur in clusters and are more common in the jejunum and ileum⁹ and thus whiskering is not commonly seen. The polyps are usually small, but thickened folds give the appearance of large polypoidal lesions. The polyps appear as multiple filling defects throughout the GI tract. Barium has now been replaced by CT and MR enterography as the preferred non-invasive investigation for polyposis syndromes due to their higher specificity and sensitivity. CT or MR enterography also demonstrates diffuse polyps throughout the stomach, duodenum, small and large bowel as well as rectum.¹⁶ Duodenum and ileocecal junction were prominently affected in our case with large polyps. Sessile polyps are usually seen as just thickening of the mucosal folds or bowel wall. Pedunculated polyps are seen as spherical homogeneously enhancing soft tissue masses of variable size, projecting into the lumen of the hollow viscera. Complications such as intussusception with polyp as the lead point may be seen leading to small bowel obstruction.

The differential diagnosis of CCS includes inflammatory bowel disease (IBD) and other polyposis syndromes (► **Table 1**) such as familial adenomatous polyposis (FAP), juvenile polyposis syndrome, Peutz–Jeghers syndrome, Gardner and Cowden syndrome.¹⁷ IBD frequently presents with diarrhea and abdominal pain with extraintestinal manifestations, but lacks diffuse polypoidal growth, especially in

the stomach. CCS and IBD share similar clinical presentations but differ in the radiological appearances by the presence of polyps in the former and ulceroconstrictive lesions in the latter. Various imaging signs such as comb sign, fat halo sign, mural wall hyperenhancement, and wall thickening help in establishing the diagnosis of IBD.^{18,19} Most of the polyposis syndromes can be differentiated by the age of the patient, family history, distribution of the polyps, and extraintestinal manifestations (► **Table 1**).¹⁵ The gastric rugal thickening of CCS may mimic Menetrier’s disease or lymphoma. However, the presence of colonic polyps and the absence of enlarged lymph nodes make CCS more likely in the present case.

Endoscopy shows multiple polyps that coalesce and give a mass-like appearance with thickened edematous mucosa throughout the GI tract.²⁰ Biopsy shows features of benign juvenile-like or hamartomatous polyps, mild infiltration of inflammatory cells including eosinophils, massive submucosal edema mostly located in the lamina propria, hyperplasia of the foveolar epithelium, focal hyperplastic features, and cystic dilation of the mucosal glands.¹⁷ In CCS, the mucosa shows edema, congestion, and inflammation differentiating it from the mucosa in juvenile polyposis where it is normal.⁶

Although no medical therapy is curative, some therapies such as hyperalimentation, corticosteroids, H2-receptor antagonists, antibiotics, cromolyn sodium, anabolic steroids, surgery, and combinations of these therapies have demonstrated improvement in symptoms and a decrease in polyp burden.⁶

In conclusion, Cronkhite–Canada syndrome is a rare multisystem disorder, characterized by gastrointestinal polyposis and malabsorption. The characteristic clinical, radiological, and endoscopic findings help in suggesting a diagnosis. Histology is confirmatory.

Conflict of Interest

None declared.

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