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CASE REPORT | ENDOSCOPY

Cronkhite-Canada Syndrome: A Rare Cause of Gastrointestinal Polyposis With Response to Emerging Therapy

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ABSTRACT

A 70-year-old man presented to the clinic with a 6-month history of dysgeusia, followed by chronic, non-bloody diarrhea and 45 lb unintentional weight loss. Esophagogastroduodenoscopy discovered confluent nodularity in the gastric antrum and examined duodenum, but a normal esophagus. Colonoscopy uncovered patches of polypoid nodular mucosa throughout the entire colon. Biopsies of the nodular mucosa were consistent with hamartomatous polyps while biopsies of the intervening, normal-appearing mucosa demonstrated edema with crypt architectural distortion. Other hereditary polyposis syndromes were excluded with genetic testing, confirming a diagnosis of Cronkhite-Canada syndrome. Adalimumab therapy was initiated with clinical improvement after nonresponse to prednisone.

INTRODUCTION

Cronkhite-Canada syndrome (CCS) is a rare non-hereditary polyposis syndrome with an estimated incidence of one per 1 million.[1] It predominantly affects male individuals, with a male-to-female ratio of approximately 3:2, and it typically manifests in the sixth decade of life.[2] Its diagnosis mainly depends on typical clinical manifestations, endoscopic findings, and histological features. Clinical characteristics include skin hyperpigmentation, alopecia, and onychodystrophy and gastrointestinal manifestations including abdominal pain, chronic diarrhea, polyposis, and protein losing enteropathy, all of which lead to anorexia and malnutrition.[3] The polyps involve the entire gastrointestinal tract sparing only the esophagus. Histologically, the polyps are hamartomatous and the intervening endoscopically normal-appearing mucosa also has evidence of edema and chronic injury. The etiology of CCS is unknown, although it is believed to be immune-mediated. As such, treatment mostly consists of systemic steroids. Nevertheless, the estimated 5-year mortality of CCS is very high at 55% emphasizing the need for early recognition and novel effective therapy.[4] In this report, we discuss a unique presentation of steroid-refractory CCS, treated successfully with adalimumab.

CASE REPORT

A 70-year-old man with history of gastroesophageal reflux disease presented with a 6-month history of dysgeusia and chronic, non-bloody diarrhea up to 12 times per day. Associated symptoms included nausea, onycholysis, and a 45 lb unintentional weight loss since symptom onset. The patient denied taking supplements, over-the-counter medication including nonsteroidal anti-inflammatory drugs, or prescription medication other than omeprazole as needed. Family and social history, including travel, were noncontributory.

Upon presentation, the patient was afebrile, neither tachycardic nor tachypneic, with a blood pressure of 96/56 and oxygen saturation of 98% on room air. His body mass index was 21 kg/m^2. General examination revealed bitemporal and supraclavicular wasting and a general lack of muscle definition. Dermatologic examination revealed significant onychodystrophy and well-defined hyperpigmented macules along the lower extremities. The abdomen was scaphoid, otherwise unremarkable.

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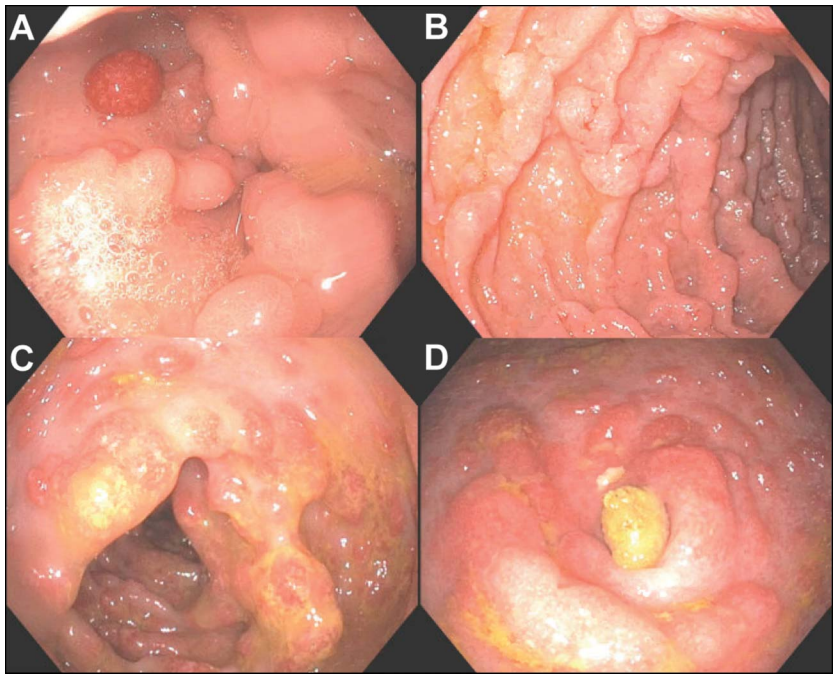

Figure 1. Endoscopic imaging at the time of diagnosis. (A) Edematous and nodular gastric antrum with polypoid features. (B) Edematous and nodular duodenal bulb and second portion of the duodenum with polypoid features. (C) Transverse colon with moderate-to-severe erythema and edema with increased polypoid burden compared with the left colon. (D) Appendiceal orifice surrounded by multiple sessile polypoid lesions.

Serum analysis was notable for normocytic anemia (hemoglobin 10.1 g/dL, mean corpuscular volume 99.7 fL), hyponatremia (134 mEq/L), and hypoalbuminemia (1.9 g/dL). Remaining components of the complete blood count and comprehensive metabolic panel, including renal function and transaminases were within normal limits. Stool analyses were notable for elevated fecal calprotectin (1,840 mcg/g), elevated total alpha-1 anti-trypsin (270 mg/dL), stool osmolar gap of 70 mOsm/kg, and negative for common microbial infections.

Diagnostic computed tomography enterography revealed pancolonic thickening and unremarkable small bowel. Esophagogastroduodenoscopy discovered edema and confluent nodularity in the gastric antrum and entire examined duodenum, with a normal esophagus (Figure 1). Colonoscopy noted patchy moderate inflammation and polypoid nodular mucosa throughout the entire colon (Figure 1) while the terminal ileum appeared normal. Biopsies of the nodular mucosa were consistent with hamartomatous polyps characterized by architectural distortion, increased lamina propria lymphoplasmacytic inflammation, and foci of neutrophilic crypt and surface epithelial injury. Biopsies of the intervening, endoscopically normal-appearing mucosa demonstrated architectural distortion, lamina propria edema, and a mild increase in lamina propria inflammation (Figure 2). Other hereditary polyposis syndromes were excluded after germline analysis using an expanded next-generation multigene panel test (Invitae Multi-cancer panel, 84 cancer predisposition genes). Based on these findings, a clinical diagnosis of CCS was made. Shortly after, the patient was initiated on steroid therapy with prednisone 40 mg daily and initiated on total parenteral nutrition to acutely address malnutrition. Despite 6 weeks of

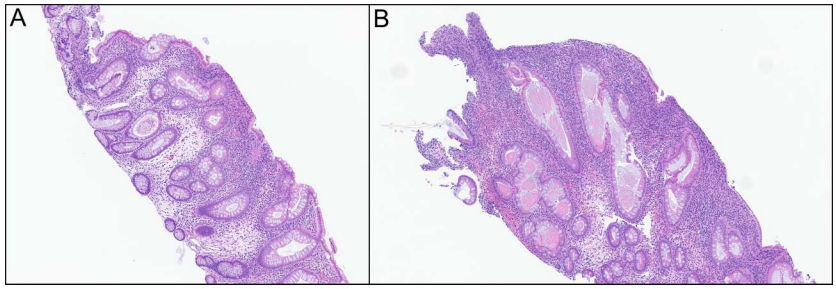

Figure 2. Colonic biopsies at the time of diagnosis. (A) Colon biopsy from the endoscopically normal-appearing right colon demonstrating crypt distortion, lamina propria edema, and increased lamina propria lymphoplasmacytic inflammation (hematoxylin and eosin, 100×). (B) Biopsies from the polypoid mucosa demonstrating crypt distortion, dilated colonic crypts, increased lymphoplasmacytic inflammation within the lamina propria, and foci of surface epithelial injury (hematoxylin and eosin, 100×).

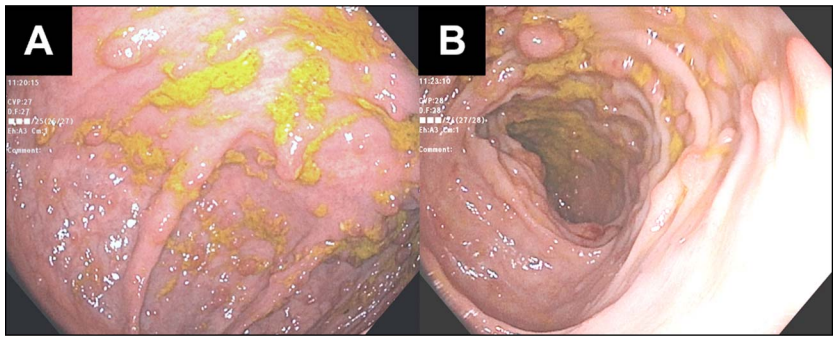

Figure 3. Endoscopic imaging after 6 months of adalimumab therapy. (A) Ascending colon and (B) transverse colon with reduced erythema and edema, a more apparent vascular pattern, and decreased polypoid burden compared with the colon at the time of diagnosis.

high-dose steroids, his symptoms were not improving while his weight continued to decrease. He was subsequently initiated on anti-tumor necrosis factor therapy with subcutaneous adalimumab.

After 6 months of treatment, the patient improved as noted by a marked reduction in frequency of bowel movements (2–3 per day), increase in weight by 4.9 kg (current body mass index 25 kg/m^2), normalization of serum albumin (3.8 g/dL), and a decrease in fecal calprotectin (198 mcg/g). He was weaned off of total parenteral nutrition, and repeat colonoscopy showed marked resolution of inflammation in the right colon in addition to reduced polyp burden throughout the colon (Figure 3). To ensure optimization of adalimumab therapy, serum levels and autoantibodies were checked, revealing a therapeutic level of 8.2 mcg/mL and no detectable antibodies.

DISCUSSION

Although CCS was first described in 1955, it remains extremely rare, and as such, large studies evaluating pathogenesis and medical treatment still do not exist.[3,5] Most occurrences are reported in the literature as case reports or case series. Those affected are usually of European or Asian descent, with approximately 75% of cases worldwide coming from Japan.[6] The average age at presentation is 59 years, but more than 80% of patients are older than 50 years at the time of diagnosis.[5] The patient discussed above is of European descent and was 70 years at the time of presentation.

Given the high degree of morbidity associated with the disease, early consideration and diagnosis becomes of utmost importance. While no specific criteria for diagnosis have been established, it depends on a combination of clinical manifestations including ectodermal abnormalities, endoscopic findings, and histological features. Considering most reported cases of CCS have initially presented with symptoms of chronic diarrhea, anorexia, and weight loss, the onus for diagnosis is shouldered primarily by gastroenterologists.[2,3] Interestingly, our patient first developed dysgeusia. Only a few months after the development of these symptoms did the patient begin to experience diarrhea and weight loss.

The etiology, pathogenesis, and optimal treatment are yet to be determined. Case series have shown significantly increased immunostaining for autoimmune-related immunoglobulin G4 antibody and immunoglobulin G4-positive plasma cells in CCS polyps compared with those in juvenile polyposis syndrome and normal control tissue.[7,8] One case demonstrated strong intracellular expression of tumor necrosis factorα activity in small intestinal mucosal biopsies.[9] Moreover, reported cases have demonstrated some response to corticosteroid therapy or tumor necrosis factorα inhibition.[7,10–14] Several case reports include concurrent diagnoses of vitiligo, membranous nephropathy, hypothyroidism, and elevated antinuclear antibody titers.[6,15–18] These comorbidities, serologic and histologic findings, and treatment responses are suggestive of a potential autoimmune mechanism underlying CCS. Uniquely, the patient discussed above did not demonstrate clinical response to oral prednisone and, therefore, was transitioned to biologic therapy with adalimumab.

Despite 7 decades since CCS was first described, there remains much to learn. This case sheds light on a rare but real disease and proposes a potential therapy for steroid-refractory patients.

DISCLOSURES

Author contributions: K. Khadarian: wrote the manuscript, treated the patient; R. Pai: reviewed pathology; NJ Samadder: edited the manuscript, performed endoscopy, treated the patient. K. Khadarian is the article guarantor.

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REFERENCES

1. Zhao R, Huang M, Banafea O, et al. Cronkhite-Canada syndrome: A rare case report and literature review. *BMC Gastroenterol.* 2016;16:23.
2. Goto A. Cronkhite-Canada syndrome: Epidemiological study of 110 cases reported in Japan. *Nihon Geka Hokan.* 1995;64(1):3–14.
3. Cronkhite LW Jr, Canada WJ. Generalized gastrointestinal polyposis; an unusual syndrome of polyposis, pigmentation, alopecia and onychotrophia. *N Engl J Med.* 1955;252(24):1011–5.

4. Daniel ES, Ludwig SL, Lewin KJ, Ruprecht RM, Rajacich GM, Schwabe AD. The Cronkhite-Canada Syndrome. An analysis of clinical and pathologic features and therapy in 55 patients. *Medicine (Baltimore).* 1982;61(5):293–309.
5. Slavik T, Montgomery EA. Cronkhite-Canada syndrome six decades on: The many faces of an enigmatic disease. *J Clin Pathol.* 2014;67(10):891–7.
6. Firth C, Harris LA, Smith ML, Thomas LF. A case report of Cronkhite-Canada syndrome complicated by membranous nephropathy. *Case Rep Nephrol Dial.* 2018;8(3):261–7.
7. Sweetser S, Ahlquist DA, Osborn NK, et al. Clinicopathologic features and treatment outcomes in Cronkhite-Canada syndrome: Support for autoimmunity. *Dig Dis Sci.* 2012;57(2):496–502.
8. Li Y, Luo HQ, Wu D, et al. Clinicopathologic features of Cronkhite-Canada syndrome and the significance of IgG4-positive plasma cells infiltration [in Chinese]. *Zhonghua Bing Li Xue Za Zhi.* 2018;47(10):753–7.
9. Martinek J, Chvatalova T, Zavada F, Vankova P, Tuckova I, Zavoral M. A fulminant course of Cronkhite-Canada syndrome. *Endoscopy.* 2010;42(-Suppl 2):E350–351.
10. Samadder NJ, Valentine JF, Affolter K. A rare cause of diarrhea and polyposis. *Gastroenterology.* 2017;153(6):1490–1.
11. Liu S, You Y, Ruan G, et al. The long-term clinical and endoscopic outcomes of Cronkhite-Canada syndrome. *Clin Transl Gastroenterol.* 2020;11(4):e00167.
12. Jiang CD, Myint H, Tie A, Stace NH. Sustained clinical response to infliximab in refractory Cronkhite-Canada syndrome. *BMJ Case Rep.* 2020; 13(12):e236990.
13. Salman Roghani R, De Castro J, Ajumobi AB. Clinical and endoscopic response to anti-tumor necrosis factor-alpha antibody therapy in a patient with Cronkhite-Canada syndrome. *J Investig Med High Impact Case Rep.* 2023;11:23247096231179451.
14. Taylor SA, Kelly J, Loomes DE. Cronkhite-Canada syndrome: Sustained clinical response with anti-TNF therapy. *Case Rep Med.* 2018;2018: 9409732.
15. Choi YJ, Lee DH, Song EJ, Kim JW, Chae HS. Vitiligo: An unusual finding in Cronkhite-Canada syndrome. *J Dermatol.* 2013;40(10):848–9.
16. Onozato Y, Sasaki Y, Abe Y, et al. Cronkhite-Canada syndrome associated with gastric outlet obstruction and membranous nephropathy: A case report and review of the literature. *Intern Med.* 2020;59(22): 2871–7.
17. Takeuchi Y, Yoshikawa M, Tsukamoto N, et al. Cronkhite-Canada syndrome with colon cancer, portal thrombosis, high titer of antinuclear antibodies, and membranous glomerulonephritis. *J Gastroenterol.* 2003; 38(8):791–5.
18. Qiao M, Lei Z, Nai-Zhong H, Jian-Ming X. Cronkhite-Canada syndrome with hypothyroidism. *South Med J.* 2005;98(5):575–6.