Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/mjafi

Case Report

Panendoscopic characterization of Cronkhite–Canada syndrome

Ashish Kumar Jha^{a,*}, Amarendra Kumar^b, Sanjeet Kumar Singh^c,
Richa Madhawi^d

^a Assistant Professor (Gastroenterology), Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India

^b Professor (Gastroenterology), Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India

^c Assistant Professor (Pathology), Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India

^d Assistant Professor (Radiation Oncology), Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India

ARTICLE INFO

Article history:

Received 15 December 2016

Accepted 13 March 2017

Available online 18 April 2017

Keywords:

Cronkhite–Canada syndrome

Panendoscopy

Single balloon enteroscopy

Polyp

Helicobacter pylori

Introduction

Cronkhite–Canada syndrome (CCS) is rare non-familial disorder of unknown etiology, characterized by gastrointestinal cystic polyposis and ectodermal manifestations. Less than 500 cases have been reported in the world literature so far, and most of these cases were reported from Japan.^{1–3} Only a handful of cases of CCS have been reported in this part of the

world.^{3–5} Here, we describe the clinical features and panendoscopic findings of a patient with CCS.

Case report

A 68-year-old male patient presented with a 3-month history of hypogeusia, anorexia, alopecia, generalized hyperpigmentation, and 15-kg weight loss. Physical examination revealed generalized hyperpigmentation, onychodystrophy (Figs. 1 and

* Corresponding author:.

E-mail address: ashishjhabn@yahoo.co.in (A.K. Jha).

<http://dx.doi.org/10.1016/j.mjafi.2017.03.007>

0377-1237/© 2017 Published by Elsevier B.V. on behalf of Director General, Armed Forces Medical Services.

2A) and partial alopecia. Routine blood investigations were normal. Blood tests for Addison's disease, thyroid disease and celiac disease were normal. Patient had negative result on antinuclear antibody (ANA) testing. Abdominal ultrasonography and chest radiograph were normal. CT-scan showed concentric thickening of gastric antrum, pylorus and duodenum (D1). Esophagogastroduodenoscopy (EGD) showed hypertrophy of gastric folds and polypoidal lesion in gastric antrum. EGD also showed partial atrophy and scalloping of duodenal folds. Gastric biopsies revealed edema, infiltration by lymphoplasmacytic cells and eosinophils and myxoid expansion of muscularis propria and submucosal cystic dilations. *H. Pylori* organism was seen in gastric biopsies. Patient was treated with 2-weeks of anti-*H. Pylori* therapy (clarithromycin, amoxicillin, and pantoprazole) followed by 6-weeks of PPI therapy. There was an improvement in symptoms such as dyspepsia, anorexia and hyperpigmentation. But, the patient

developed watery diarrhea. Stool examination including assay for *Clostridium difficile* toxin was normal. Repeat EGD revealed partial improvement in endoscopy appearances. Eradication of *H. Pylori* was confirmed in repeat gastric biopsies. Single balloon enteroscopy further disclosed partial atrophy in the jejunal folds (Fig. 3). Ileocolonoscopy revealed multiple sessile polyps located throughout the colon (maximum size 1.5 cm; some with a strawberry-like appearance), nonspecific colitis, and occasional tiny ulcerations and mucosal congestion of ileum (Figs. 4 and 5). Duodenal biopsies showed complete villous atrophy, hyperplasia of crypt and normal intraepithelial lymphocyte cells. Edema, lymphoplasmacytic and eosinophilic infiltration and myxoid expansion of muscularis propria were noted in biopsies from stomach, duodenum and colon (Fig. 6A). Colonic polyp biopsies revealed sessile polyps with variably sized cystically dilated glands suggestive of juvenile/hamartomatous polyp (Fig. 6B).

Patient was diagnosed as CCS, and treated with systemic steroid therapy (oral prednisolone 40 mg daily, tapered down slowly during a period of 2-months to 20 mg), proton pump inhibitors (PPI), and nutritional support. Nine-months later, substantial symptomatic improvement noted in the patient's condition such as resolution of diarrhea, improvement of the skin hyperpigmentation, increase in appetite, and regrowth of his hair (Fig. 2B). However, minimal improvement in nail dystrophy was seen. Repeat EGD and colonoscopy showed significant improvement of endoscopic findings (Figs. 7 and 8).

Fig. 1 – Onychodystrophy of fingernails.

Discussion

The Cronkhite–Canada syndrome was first described in 1955 by Cronkhite and Wilma Jeanne Canada.⁶ The mean age of onset is estimated to be in the 5th–6th decade with a male: female ratio of 1.3–2.3:1. It is a disease with bad prognosis and a

Fig. 2 – Hyperpigmentation before (A) and after treatment (B), note post-traumatic deformed middle finger.

Fig. 3 – (A) Gastric fold hypertrophy with strawberry-like appearances, (B) proximal jejunum showing partial atrophy and scalloping of folds.

Fig. 4 – Colonic sessile polyps (strawberry-like appearances right panel); congested interpolyp mucosa and partial loss of vascularity (left panel).

Fig. 5 – (A) Ileal mucosal congestion and tiny ulcer (arrow), (B) erythematous mucosa of cecum.

high mortality rate (5-year mortality rate up to 50-55%). Clinical course of CCS is progressive with occasional spontaneous remissions and frequent relapses. Gastrointestinal malignancies can be associated with CCS in up to 15% of patients; therefore aggressive screening is warranted in these patients. Whether malignant lesions arise from preexisting

polyps or coincidentally are still a controversial issue. Colon followed by stomach is most common site of cancers.^{2,3}

The cause of CCS is unknown. Current evidence is suggestive of immune mediated etiopathogenesis of disease.⁷ Clinical manifestations include chronic diarrhea, malnutrition, abdominal pain, weight loss, protein losing enteropathy,

Fig. 6 – HPE of gastric biopsies (6-A) shows edematous lamina propria with mixed inflammatory infiltrates mainly mononuclear lymphocytes, plasma cells (arrow heads) and few eosinophils (arrows) (H&E staining, magnification 400×); HPE of colonic polyp biopsies (6-B) shows expanded lamina propria with mixed inflammatory infiltrates, variably sized glands and cystically dilated glands (H&E staining, magnification 40×).

Fig. 7 – Recovery of gastric mucosa; (A) white light endoscopy and (B) narrow band imaging.

Fig. 8 – Recovery of colonic polyp; (A) white light endoscopy and (B) narrow band imaging.

dystrophic changes in the fingernails, alopecia and cutaneous hyperpigmentation. The laboratory abnormalities in patients with CCS are non-specific and include anemia, hypoproteinemia, hypocalcaemia, hypomagnesaemia and hypokalaemia. Raised serum ANA and IgG4 levels may be seen in CCS. Immunostaining for the anti-IgG4 antibody is significantly increased in CCS polyps compared to normal control tissues. Our patient had normal ANA level; however, we did not assess serum IgG4 levels.

The polyps (some with a strawberry-like appearance) are characteristically distributed throughout the entire gastrointestinal tract except esophagus. Gastric folds hypertrophy or folds atrophy with polypoidal lesions (carpet-like polyposis of the stomach) are characteristic changes seen in stomach. Folds atrophy, scalloping or nodularity is the features of small bowel involvement. Non-specific colitis may be present in interpolyp area of colon.

Microscopic examinations of polyps mostly show typical features of hyperplastic, benign juvenile-like or hamartomatous polyps. Adenomatous changes may be seen uncommonly in patients of CCS. Histopathological examination of non-polypoid biopsies comprises edema, impaired architecture of crypts, including dilation and branching, and presence of mixed inflammatory infiltrate composed of lymphocytes, plasma cells, and eosinophils. Histological findings include a myxoid expansion of the lamina propria, and increased eosinophils may be seen in the polyps and non-polypoidal tissues. In our patient, gastroduodenal biopsies showed villous atrophy, myxoid expansion of the lamina propria, and eosinophils infiltration. The differential diagnosis for blunted villi with a dense infiltrate of eosinophils on duodenal biopsy includes eosinophilic gastroenteritis, celiac sprue, vasculitis, parasitic infections, and lymphoma.⁸

The diagnosis of CCS is based on clinical presentations, family history, polyp distribution, polyp histology, histology of intervening (endoscopically spared or non-polypoid) mucosa and molecular genetic testing. The differential diagnosis of CCS in a patient presenting with diffuse GI polyposis includes juvenile polyposis, Peutz-Jeghers syndrome, Cowden syndrome, Turcot syndrome and familial adenomatous polyposis. An infiltrative neoplastic diseases (lymphoma or diffusely invasive carcinoma) or infectious pathology may be suspected in a patient who presents with diffusely thickened or atrophic gastric/duodenal mucosa rather than GI polyposis. Menetrier's disease should also be considered in differential diagnosis of patient presenting with diffusely thickened gastric mucosal folds with selective sparing of the lower GI tract.⁹

Treatment of CCS is still uncertain. Various treatment regimens have been described for management of CCS including corticosteroids, nutritional therapy, proton pump inhibitors, histamine H2 receptor antagonists, eradication of *H. pylori*, anabolic steroids, 5-aminosalicylate acid, cromolyn sodium, anti-tumor necrosis factor α (TNF- α) agents and immunomodulators such as cyclosporine, tacrolimus and azathioprine.^{2,3} Combination therapy (steroids with or without azathioprine, PPI and nutritional therapy) are considered the mainstay of medical treatment.³ The recommended dose and duration of therapy is also varied widely. Combination therapy consisting of oral prednisolone (dose ranges from 20 to 60 mg/day) are usually recommended for 1-year. Clinical improvement and polyp regression are usually apparent within 1-year.

Steroid-sparing agents are often required to prevent the relapse of symptom during a steroid taper. Our case showed no relapse of symptom during steroid tapering. Hence, we did not use azathioprine in our patient. Surgery may be required in patients with bowel complications such as severe protein-losing enteropathy, persistent haematochezia, malignant transformation and heavy polyp burden.

Association of *H. pylori* infection with CCS have been described in literature.^{2,10} In a study, Watanabe et al. have showed *H. pylori* infection in 54% patients of CCS (N = 113). Endoscopic remission or response attained in 53.3% of patients treated with anti-*H. pylori* therapy.² As we have observed in this patient, partial response to anti-*H. pylori* therapy may cause initial diagnostic confusion in patients presented without diarrhea.

In conclusion, CCS is extremely rare disease with a high mortality rate. A thorough and careful evaluation of a patient with GI polyposis is warranted to avoid misdiagnosis of CCS. Panendoscopy or colonoscopy is useful in patient with endoscopic evidence of diffusely thickened gastric mucosa or gastric polypoidal lesion without a conclusive histological diagnosis.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Goto A. Cronkhite-Canada syndrome: epidemiological study of 110 cases reported in Japan. *Nihon Geka Hokan*. 1995;64(1):3–14.
2. Watanabe C, Komoto S, Tomita K, et al. Endoscopic and clinical evaluation of treatment and prognosis of Cronkhite-Canada syndrome: a Japanese nationwide survey. *J Gastroenterol*. 2016;51(4):327–336.
3. Kopacova M, Urban O, Cyrany J, et al. Cronkhite-Canada syndrome: review of the literature. *Gastroenterol Res Pract*. 2013;2013:856873.
4. Patil V, Patil LS, Jakareddy R, Verma A, Gupta AB. Cronkhite-Canada syndrome: a report of two familial cases. *Indian J Gastroenterol*. 2013;32(2):119–122.
5. Sreedharanunni S, Paulose R, Jojo A, Dhar P, Gangadharan P. Colonic polyposis syndromes – an experience from a tertiary centre in South India. *Indian J Gastroenterol*. 2015;34(3):233–239.
6. Cronkhite Jr LW, Canada WJ. Generalised gastrointestinal polyposis—an unusual syndrome of polyposis, pigmentation, alopecia and onychotrophia. *N Engl J Med*. 1955;252(24):1011–1015.
7. Sweetser S, Ahlquist DA, Osborn NK, et al. Clinical pathologic features and treatment outcomes in Cronkhite-Canada syndrome: support for autoimmunity. *Dig Dis Sci*. 2012;57(2):496–502.
8. Anderson RD, Patel R, Hamilton JK, Boland CR. Cronkhite-Canada syndrome presenting as eosinophilic gastroenteritis. *Proc (Bayl Univ Med Cent)*. 2006;19(3):209–212.
9. Slavik T, Montgomery EA. Cronkhite-Canada syndrome six decades on: the many faces of an enigmatic disease. *J Clin Pathol*. 2014;67(10):891–897.
10. Okamoto K, Isomoto H, Shikuwa S, Nishiyama H, Ito M, Kohno S. A case of Cronkhite-Canada syndrome: remission after treatment with anti-helicobacter pylori regimen. *Digestion*. 2008;78(2–3):82–87.