Rare disease

Diarrhoea, weight loss and polyposis: think Cronkhite-Canada syndrome

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Correspondence to Dr Elie Aoun, eaoun@wpahs.org**Summary**

A 71-year-old male presented with nausea, diarrhoea and weight loss. He had mild to moderate alopecia, paucity of eyebrow hair, erythematous non-pruritic nodular rash on the wrists, toenail onychomycosis and scalp hyperpigmentation. A colonoscopy revealed an irregular, haemorrhagic 5 cm rectosigmoid mass. Biopsies revealed mucin distended glands and focal ischemic changes. A CT scan showed numerous polypoid-like lesions in the stomach. Upper endoscopy showed mucosal erythema and nodularity with polypoid-like lesions. Biopsies showed cystic glandular dilatation, lamina propria oedema and chronic inflammation consistent with Cronkhite-Canada syndrome (CCS). The patient was started on nutrition supplementation. His skin manifestations were treated topically and with mineral supplements. He improved within 10 weeks and is currently asymptomatic. A high index of suspicion for CCS should exist in patients who present with weight loss, diarrhoea and polyposis. If diagnosed early, the disease can be treated with the goal of clinical remission.

BACKGROUND

Cronkhite-Canada syndrome (CCS) is a rare, non-familial, non-hereditary, hamartomatous polyposis syndrome that is marked by epithelial abnormalities within the gastrointestinal tract and epidermis. Although originally described in 1955 and despite multiple cases being reported in the literature, the exact aetiology and pathophysiologic mechanisms underlying the disease remain largely unclear and poorly understood.¹ The current case highlights the importance of distinguishing and appropriately diagnosing this condition, which if caught in time and treated appropriately, can result in clinical remission.

CASE PRESENTATION

A 71-year-old male patient with a medical history significant for diabetes mellitus and hypertension presented with nausea, diarrhoea and an unexplained 15 pound weight loss over a 1-month period. The diarrhoea was described as watery, non-bloody, with about five to six episodes daily and occasional nocturnal occurrences. The patient denied any vomiting and had no significant change in appetite. There were no fevers or chills reported. He had undergone multiple screening colonoscopies, the last of which was approximately 5 years prior to presentation and was reportedly normal.

INVESTIGATIONS

On physical examination, the patient was noted to have mild to moderate alopecia and paucity of eyebrow hair. His skin examination was significant for an erythematous non-pruritic nodular rash on the wrists. The examination was also significant for onychomycosis of the toenails and hyperpigmentation of the scalp. The abdominal examination was unremarkable. Initial blood work, which included a complete blood count, a basic metabolic panel,

liver function tests and celiac serologies, were all within normal limits. Stool studies were negative for ova and parasites, *Clostridium difficile*, stool white blood cell and culture. The patient continued to have symptoms, and a colonoscopy was performed revealing an irregular, haemorrhagic appearing, umbilicated, soft 5 cm mass about 20 cm from the anal verge (figure 1). Biopsies revealed rectal mucosa with mucin distended glands and focal ischemic changes. There was no evidence of underlying malignant changes on histology. The patient was then referred to colorectal surgery for further evaluation. Three-core biopsies performed with alligator forceps were consistent with the first set obtained during the colonoscopy. A CT scan of the abdomen and pelvis was performed showing numerous polypoid-like lesions in the gastric body and antrum up to 2 cm in size (figure 2). An upper endoscopy was then performed and showed an erythematous and nodular gastric mucosa with polypoid-like lesions (figure 3).

DIAGNOSIS

The histologic evaluation of biopsy specimens showed cystic glandular dilatation and lamina propria oedema and chronic inflammation consistent with CCS (figure 4). These findings prompted a review of the pathology slides obtained during the colonoscopy, and the pathologist concluded that these were also consistent with CCS.

TREATMENT

The patient was started on nutrition supplementation after being evaluated by a clinical nutritionist. Multivitamin and zinc supplements were initiated, and caloric supplementation was achieved by high caloric milkshakes twice daily. He was followed by a dermatologist, and his skin manifestations were treated with a combination of topical agents and mineral supplements.

Figure 1 Irregular, haemorrhagic appearing, umbilicated, soft 5 cm mass about 20 cm from the anal verge seen on colonoscopy.

OUTCOME AND FOLLOW-UP

Clinically, the patient improved within 10 weeks with a gradual decrease in his diarrhoea and nausea and slow regaining of weight. Both his alopecia and rash resolved over a period of 4 months. Repeat endoscopy and colonoscopy showed a decrease in the number of polyps with a few scattered small lesions remaining. Biopsies did not show any evidence of dysplasia. He currently is asymptomatic and continues regular follow-up with us in the outpatient setting.

DISCUSSION

Most experts consider CCS to be a rare, sporadic and acquired polyposis of the gastrointestinal tract with extra-intestinal manifestations including alopecia, cutaneous hyperpigmentation and nail dystrophy (thinning, splitting and onycholysis).² Although the majority of the published cases originate from Japan, the disease has been described in all ethnic groups. The mean age of symptom onset is 59 years, and there is a slight male predominance, with a male to female ratio of 3:2. The initial presentation usually consists of diarrhoea mainly secondary to protein loss.

In addition, patients can present with weight loss, peripheral oedema and variable degrees of fat and disaccharide malabsorption. Hypogeusia has also been reported as an early symptom. In 1995 Goto *et al* proposed a classification scheme subdividing CCS patients into five groups based on the predominant symptom (table 1).³ It was postulated that patients with dermal hyperpigmentation have the worst prognosis with an estimated 5-year mortality of 55%. Rare cases of complications associated with CCS have been reported including life-threatening gastrointestinal bleeding, intussusception, rectal prolapse and co-existing autoimmune conditions like glomerulonephritis.³

The polyps which represent the hallmark of the disease can affect the entire gastrointestinal tract with the exception of the oesophagus. These polypoid lesions are usually considered as non-neoplastic retention or inflammatory polyps rather than true neoplastic lesions despite the association of CCS with a variety of gastrointestinal cancers. All CCS polyps are sessile, and for the most part, histologic features include oedema in the lamina propria.⁴ Differentiating CCS polyps from juvenile polyps can be histologically difficult as they share similar characteristics

Figure 2 CT scan of the abdomen and pelvis showing numerous polypoid-like lesions in the gastric body and antrum up to 2 cm in size (arrowheads).

Figure 3 Upper endoscopy showing polypoid-like lesions (A) and diffuse erythema with nodularity of the gastric mucosa (B).

including cystic dilation of the glands without atypia. One main difference, which may help in this differentiation, is the oedema and congestion and the inflammation in the lamina propria usually seen in the mucosa between polyps in cases of CCS. Due to these main similarities, the diagnosis cannot be solely based on histologic features; rather, they need to encompass the whole clinical presentation and extra-intestinal manifestations as well.⁵

The differential diagnosis of CCS is wide and includes hereditary and non-hereditary polyposis syndromes. Familial adenomatous polyposis is an important autosomal dominant syndrome to exclude. It arises due to germline mutations of the adenomatous polyposis coli gene, and in general, these patients inevitably develop colorectal cancer unless their colon is resected.⁶ Juvenile polyposis is another autosomal dominant syndrome with high incidence of

Figure 4 Histological image of colon polyp showing cystic glandular dilatation, lamina propria oedema and chronic inflammation.

Table 1 Suggested classification of Cronkhite-Canada syndrome

Type	Predominant symptom
1	Diarrhoea
2	Dysgeusia
3	Thirst and abnormal sensation in the mouth
4	Abdominal symptoms other than diarrhoea
5	Alopecia

colorectal neoplasia; however, it is usually diagnosed at a much earlier age than CCS.⁷ Cowden's syndrome also affects the gastrointestinal tract through numerous inflammatory or hamartomatous polyps, but typically, there is concomitant involvement of the thyroid (70% of cases). These patients tend to have multiple facial trichilemmomas around the mouth, nose and/or eyes.⁸ Finally, Peutz-Jeghers syndrome results from mutations in the serine threonine kinase 11 gene and has typical brown melanin pigmentation on the lips and buccal mucosa.⁹ While histologically the polyps associated with the above syndrome may have very similar characteristics, the associated symptoms and organ systems involved make it easier to differentiate them from CCS.

There is no standardised treatment for this condition as there are no controlled medical trials, likely due to its rare occurrence. A variety of treatments including nutrition support, systemic corticosteroids, antibiotics, histamine blockers, eradication of *Helicobacter pylori* and even surgery have been suggested; but the current management is based on case series and anecdotal reports.¹⁰

Nutritional support is very important and is often the initial step in the management of patients with CCS, especially in the setting of various levels of malabsorption of different nutrients that may lead to vitamin deficiencies. In some patients, including the case we are hereby presenting, remission may be achieved with nutrition support alone. Usually the addition of a multivitamin and zinc supplementation is needed. If patients do not respond to this intervention alone, then corticosteroids are often used.

They have been reported to induce remission in patients with CCS; however, the actual dosing regimen remains at the discretion of the treating physician due to the lack of clinical data. Like the majority of disease entities treated with steroids, the goal is to achieve remission and then taper the drug.¹¹ Re-treatment is possible in cases of relapse. More recently, two separate cases were reported to achieve remission by eradication of *H. pylori* and maintenance therapy with a proton pump inhibitor.^{12 13} Because of the diffuse involvement of the gastrointestinal system in patients with CCS, surgery is usually used to treat certain serious complications such as bleeding, malignancies and intussusception.¹⁴

CCS has been associated with a variety of gastrointestinal malignancies including gastric, colon and rectal cancers. The main debate however remains on whether those cancers arise from the actual CCS polyp or whether they occur coincidentally. Several proposed mechanisms behind increased malignancy risks have been proposed in this patient population. The presence of chronic inflammation in the lamina propria may provide a favourable background for tumorigenesis. In 2004, Yashiro *et al* suggested the possibility of a serrated adenoma to carcinoma sequence.¹⁵ A retrospective review of 25 cases of CCS noted the presence of serrated adenoma of the polypoid lesions in 10 patients (40%).¹⁵ This mechanism is supported by a higher predisposition to genetic alterations and mutation in the setting of aberrant crypt maturation and increased proliferation of serrated adenomas. Regardless of the underlying mechanisms, the association between CCS and gastrointestinal cancers is certainly real and raises significant challenges in screening and detecting those cancers. Typically multiple inflammatory polyps are present in patients with CCS, and short of excising all of them, which is neither recommended nor feasible, it would be difficult to identify polyps harbouring dysplastic or malignant changes. Although there are no guidelines with regard to screening modalities and frequencies, one possible approach would be to treat the patient with the hope of remission and then to repeat the endoscopic procedures with the plan to excise any

large (>1 cm) remaining polyps. Close surveillance procedures would also be needed, but the exact interval at which these should be performed remains uncertain with narrow intervals and yearly colonoscopies being favoured.

In summary, CCS is a rare disorder with a poorly understood aetiology and pathophysiology and an even more unclear treatment regimen. There should be a high index of suspicion for CCS in patients who present with weight loss, diarrhoea and polyposis. If diagnosed early, the disease can be treated with the goal of clinical remission.

Learning points

- ▶ CCS is a rare disorder with a poorly understood aetiology and pathophysiology.
- ▶ Symptoms associated with CCS are often non-descript, thus making the diagnosis difficult.
- ▶ Although there is no agreed upon standard of treatment, proposed management approaches include nutritional support, systemic corticosteroids, antibiotics, histamine blockers, eradication of *H pylori* and surgery.
- ▶ If the diagnosis is made in a timely manner, treatment strategies can be applied, and clinical remission may result, as was evidenced in the current case.

Competing interests None.

Patient consent Obtained.

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