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Cronkhite-Canada syndrome: case description

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ABSTRACT

We present the case of an 80-year old woman affected by the Cronkhite-Canada syndrome. This rare disease was described for the first time in 1955. It is characterized by the growth of multiple polyps in the gastroenteric tract, leading to diarrhea, alopecia, dystrophy of nails and hyper-pigmented skin. In this article, we describe the patient's clinical picture and report the results of laboratory tests and imaging assessments.

Introduction

The Cronkhite-Canada syndrome (CCS) is a rare disease characterized by generalized gastrointestinal polyps associated with hyperpigmentation, hair loss, and dystrophic changes in the fingernails. It was first reported and described by Cronkhite and Canada in 1955.[1] To date, only about 400 case reports of CCS exist in the worldwide literature. The etiology of CCS remains largely unknown. Although fatigue and mental stress are the most commonly cited potential causes, surgery, pregnancy, radiotherapy, and alcoholism have been proposed as potential contributing factors.[2] CCS is mainly diagnosed on the basis of its clinical manifestations and indicative histological findings, including generalized gastrointestinal polyps associated with ectodermal changes. Because of its rarity and lack of symptom control, the most efficacious therapy remains to be determined. In the literature, CCS treatment includes symptomatic and support therapy, administration of corticosteroids, antibiotics and acid inhibitors, therapeutic endoscopy, and surgery.

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Case Report

We report a case of an 80-year old woman, admitted to the emergency ward of our hospital and then to our internal medicine ward. She came to our Emergency Room reporting sudden heart palpitations. These symptoms occurred, while she was experiencing a diahrroic syndrome. After hospital admission, the presence of hypokalemia was detected; therefore she was supplemented with an IV potassium-chloride solution to quickly resolve the arrhythmia.

The patient's clinical history included the following symptoms: hypoageusia, dyspeptic disorders, diahrroic bowels, weight loss by about 10 kg, progressive alopecia (Figure 1) and nail dystrophy (Figure 2) with the loss of all nails in hands and feet. Therefore, the patient had already had a number of medical tests. The laboratory tests revealed mild anemia, vitamin B12 deficit, hyperphosphatemia, slightly higher levels of parathyroid hormone (PTH) and gastrin (during therapy with proton pump inhibitors). A screening program to test the presence of an autoimmune status was negative (antinuclear antibodies, C3, C4). An upper endoscopy showed that the esophagus was normal, the gastric mucosa (Figure 3) was very hyperemic, edematous, thick and grainy and there were also some converging folds close to each other towards the pylorus. A small polyp was removed for an histology report. The duodenal mucosa presented a similar macroscopic appearance. The histological report, performed on the gastric polyp showed the presence of a fundic gastric mucosa, where a chronic gastritis was observed, together with a slightly dilated cystic gland. *Helicobacter pylori* was not detected. In the duodenal specimen, histological evaluation showed chronic inflammation, gastric metaplasia, infiltration of lymphoid T cells (CD3+) and detected several enterochromaffin-like cells. Immunohistochemistry for chromogranin was positive. In order to exclude the existence of a gastrinoma, a somatostatin

receptor scintigraphy (Ocreoscan) was performed, but it was negative. Abdominal ultrasound did not show significant alterations.

An ultrasound of the neck was performed, after detection of PTH increase; however no remarkable alterations were observed.

Furthermore, the patient reported a history of osteoporosis of the spine and femur diagnosed by dual-energy X-ray absorptiometry and open-angle glaucoma.

After admission to our unit, the patient continued to receive supplementations of potassium chloride, until her values normalized. Since then the patient maintained a regular sinus rhythm and did not experience other episodes of palpitations. Blood tests showed hypokalemia, hypomagnesaemia, hypophosphoremia, reduced serum levels of zinc, vitamin B12, Vitamin D 25 OH and hypoalbuminemia (Table 1). There was a slight increase in inflammatory markers. A 24-h urine collection was performed to detect protein, potassium, phosphate and calcium urinary excretion. This test showed reduced levels of all these electrolytes. On the basis of the patient's symptoms and signs as well as the results of her serum/imaging tests and histological assessment, we supposed that she might be suffering from a CCS syndrome. Therefore a colonoscopy was requested. Endoscopic examination confirmed the presence of the typical macroscopic pattern, consistent with CCS. The endoscopic procedure detected a diffuse polyposis (with small polyps) involving in particular the transverse and right colon and the presence of numerous micro polyps in the cecum and of the ileocecal valve (Figure 4). The histological examination demonstrated the presence of an edema of the lamina propria, inflammatory infiltration of lymphocytes and cystic dilatation of the glands.

According to hypothesis of Sweetser *et al.*,[3] the levels of sub-classes of immunoglobulin IgG were measured (Table 1) and a considerable increase in the fraction of IgG4 was found. Steroid treatment with Prednisolone 50 mg/die was started and with vitamins and microelements supplementation, inducing a rapid reduction of asthenia and a quick recovery in appetite and regular bowel movements. The dosage of the steroid was gradually decreased down to a maintenance dose (5 mg/die). After about 60 days of treatment, an overall significant improvement in the patient's conditions was observed with the restoration of regular bowel movements, and a 5 kg weight gain, re-growth of hair and nails and a partial recovery of taste. Table 2 shows the reported laboratory findings after a 60-day treatment.[4]

Discussion

The Cronkhite-Canada syndrome is a rare form of gastrointestinal polyposis, described for the first time in 1955[1] and is characterized by widespread gastrointestinal polyps, ectodermal tissue alterations, such as alopecia, onychodystrophy and hyperpigmentation. To date about 500 cases have been documented and described, 75% of them in the Japanese population.[5] The

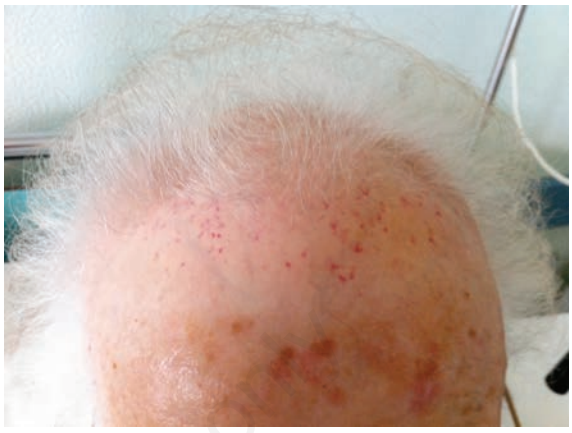

Figure 1. Alopecia.

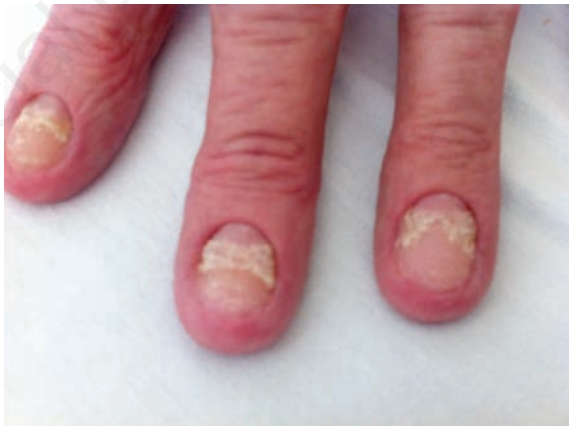

Figure 2. Nail dystrophy.

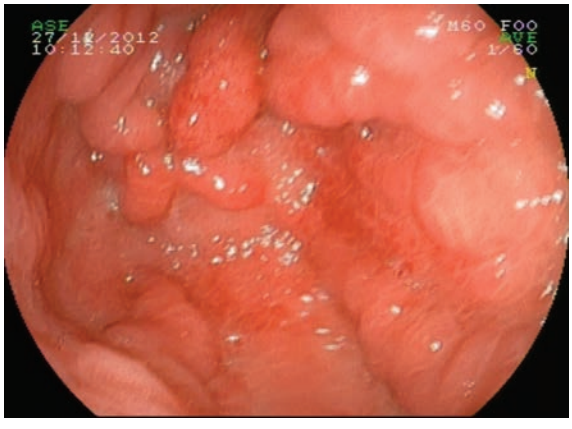

Figure 3. Gastric mucosa.

ratio between males/females is 3:2. This condition tends to occur in adult/old age, with a mean of about 60 years of age.[6]

Although fatigue and mental stress are the most commonly reported potential causes, surgery, pregnancy, radiotherapy, and alcoholism have been proposed as potential contributing factors.[2] The first most common symptoms are: dyspeptic disorders, diarrhea and change in bowel habits, hypogeusia, significant weight loss and signs (glossitis, numbness in the limbs, xerophthalmia, xerostomia), which are likely to be secondary to vitamin and mineral deficiency. According to a study, enrolling 110 patient with CCS, which was performed in the Japanese population by Goto,[2] 5 subtypes of this syndrome were described on the basis of clinical symptoms (Table 3). Our case can be classified as the uncommon variant subtype II of CCS. This condition is characterized by hypogeusia, nail dystrophy, alopecia which coexist in the absence of hyperpigmentation.

The disease is often associated with a protein-loosing enteropathy, caused by an excessive mucous secretion of the intestinal crypt cells, leading to hypoproteinemia, malnutrition and electrolyte disorders.[7] The most commonly described serum alterations are: electrolyte disorders (hypokalemia, hypomagnesemia), mineral and vitamin deficiencies (zinc, copper, selenium, vitamin A, D, E), hypoproteinemia and ipoabuminemia.[8,9]

The macroscopic characteristics of the mucosal alterations can be detected by means of endoscopic exams and include hyperemia and grainy gastric mucosa with the presence of rare hyperelastic micropolyps and the presence of multiple polyposis on the colon. The polyps are usually small (1 mm-3 cm) and mainly sessile.[10] The esophagus is usually unaffected. The typical histological feature is represented by gastritis and chronic duodenitis with gastric metaplasia involving the duodenum mucosa. The polyps (both gastric and of the colon) usually present histologic alterations, such as edema of the lamina propria, inflammatory infiltrate and cystic swelling of the glands.[7-9]

If we consider non-hereditary clinical entities, which are characterized by gastrointestinal polyps, the differential diagnosis must be done considering hyperplasic juvenile polyposis (presence of numerous polyps spread in the colon) and symptoms that can often be similar but the absence of typical ectodermal alterations, such as alopecia, hyper pigmentation and onicodistrophia, makes the diagnosis usually simple. Furthermore, one must keep in mind that the syndrome of Peutz-Jeghers, Cowden disease and adenomatous polyposis have common signs and symptoms. Appropriate laboratory and imaging tests as well as clinical assessment of patients may help differentiate these syndromes and/or diseases (Table 2).

Autoimmune mechanisms may be involved in CCS pathogenesis. A study performed by Sweetser *et al.*[3] on 14 patients of the Mayo Clinic showed the presence of high levels of immunoglobulin IgG4 (associated to autoimmune diseases) due to polyps of the colon. Our observation of increased serum IgG4 levels in this subject is consistent, although indirectly, with the hypothesis that CCS may have an autoimmune

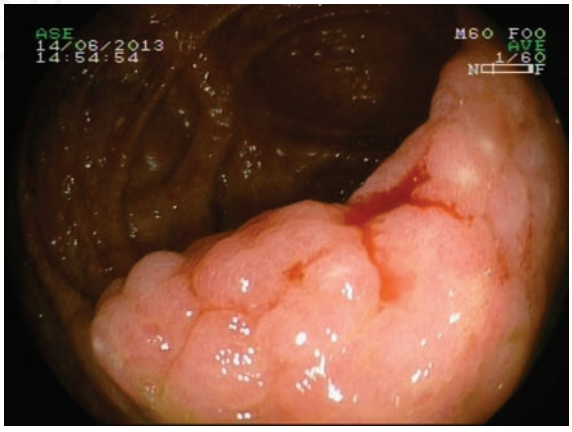

Figure 4. Colon mucosa.

Table 1. Laboratory findings.

Laboratory variable	Value	Normal range
Total protein (g/dL)	5.7	6.2-8.7
Serum albumin (g/dL)	3.16	4-4.76
25 OH vitamin D (nMol/L)	22	62-199
Vitamin B12	183	190-700
Ferritin (pMol/L)	89	54-755
Copper (uMol/L)	10.5	11.8-22
Zinc (uMol/L)	8.4	9-15.7
Potassium (mEq/L)	2.6	3.3-5.4
Magnesium (mg/dL)	1.5	1.5-2.6
Total IgG (mg/dL)	813	740-1440
IgG4 (mg/dL)	126 (15.5% of total IgG)	1.6-6.8% of total IgG

genesis. On the other hand, epidermal disturbances have not been correlated with an autoimmune origin. In a recent article it was demonstrated that hair follicles of the scalp show no evidence of histological alterations or inflammatory lesions.[11] It is therefore assumed that the ectodermal tissue alterations may be caused by malabsorption of micronutrients and minerals, such as zinc and iron.

Due to the rarity of the syndrome, the possible therapeutic strategies documented up to now are not univocal and there is no evidence-based therapy.[12] The autoimmune pathogenetic hypothesis has led many authors to use steroid therapy, resulting in a satisfactory high percentage of clinical response. Treatment scheme generally includes prednisone 40 mg for 7 days with a progressive tapering to 5 mg per week, and then it should be withdrawn. With this regimen Sweetser *et al.* obtained clinical remission after 3 months of therapy in 10/11 cases.[3] Cases of recurrences were observed, once the steroid therapy

Table 2. Differential diagnosis of polyposis colonic syndromes.

Syndrome	Age onset (years)	Transmission	Distribution of polyps	Histology	Extra-intestinal manifestation	Prognosis
Hyperplastic polyposis	>40	Autosomal Dominant	Colon	Hyperplastic polyps, sessile serrated adenomas	None	Colon cancer
CCS	50-60	Sporadic	Stomach, small bowel, colon	Hamartomatous polyps (juvenile type) exhibiting glandular hyperplasia, cystic dilation, mucosal edema, and eosinophilic inflammation	Alopecia, dermal hyperpigmentation, onychodystrophy, diarrhea, protein-losing enteropathy, dysgeusia	Cachexia, colon cancer (mostly left-sided)
Peuz-Jeghers	10-30	Autosomal Dominant	Stomach, small bowel, colon	Hamartomas in th e stomach and small bowel, adenomatous polyps in the colon	Mucocutaneous melanosis	Colon, gastric, pancreatic, breast, and/or gynecologic cancers
Familial adenomatosus polyposis	15-20	Autosomal Dominant	Stomach, small bowel, colon	Adenomas	Hypertrophy of retinal pigment epithelium, brain tumors (Turcot syndrome), epidermoid cysts, mandibular osteomas, desmoids, thyroid tumors (Gardner syndrome)	Colon, duodenal, and/or thyroid cancers
Cowden disease	9-20	Autosomal Dominant	Stomach, small bowel, colon	Hamartomas	Facial trichilemmomas, macrocephaly, mucocutaneous lesions, acral keratoses, thyroid disease, breast disease	Breast, thyroid, reproductive organ, and/or colon cancers

CCS, Cronkhite-Canada syndrome. *Adapted from Seshadri* et al., *2012.*[4]

Table 3. Laboratory findings after 2 months of treatment.

Laboratory variable	Value	Normal range
Total protein (g/dL)	6.1	6.2-8.7
Serum albumin (g/dL)	4.35	4-4.76
25 OH vitamin D (nMol/L)	45	62-199
Vitamin B12	>700	190-700
Ferritin (pMol/L)	238	54-755
Copper (uMol/L)	11.7	11.8-22
Zinc (uMol/L)	12.3	9-15.7
Potassium (mEq/L)	3.7	3.3-5.4
Magnesium (mg/dL)	2.2	1.5-2.6

was suspended or reduced. Because of this reason, alternative regimens were used, such as azathioprine 2 mg/kg/day, obtaining longer lasting positive clinical responses.[1-3,5-10,12] Other possible alternative treatments used were: H2 blockers, proton pump inhibitors, antibiotics, but with poor results and limited to patient with *H. pylori* co-infection.[13] Due to the common symptoms, such as impaired absorption, malnutrition, and immune-suppression, an appropriate nutritional support with concentrated vitamins and minerals must be added in addition to the treatment. Recent evidence suggests that a total parenteral nutrition should be planned to improve clinical outcome of these patients.[14]

There is a unanimous consensus on prevention screening programs for colorectal cancer in these patients. However, to date, no univocal results is available, explaining whether polyps, observed in subjects with CCS, are really precancerous lesions, although some studies showed that the risk of this malignancy is higher in these patients.[4] In the largest epidemiological study available to date, a rather high incidence of colon rectal cancer has been reported (71% adenomas, 14% carcinomas).[12] Unfortunately, the majority of polyps limit the possibility of performing a biopsy all these lesions. On the whole, these data strongly suggests that an adequate follow-up is required in this patient, including colonoscopy after the end of treatment. Appropriate therapy may cause the regression of inflammatory and hyperplastic polyps, making it easier to distinguish which polyps are at greater risk of neoplastic evolution.[3] Therefore, they can be removed and used for histological assessment.

Conclusions

Cronkhite-Canada syndrome is a rare, acquired gastrointestinal polyposis syndrome with a typical dermatologic manifestation. The polyps in CCS are endoscopically similar to several other polyposis syndromes, but can present some histological peculiarities. The two milestones of therapy include immunosuppression with steroids and an appropriate nutritional support. There is evidence for an increased risk of colorectal neoplasia, but the early detection of this malignancy is difficult, therefore decisions concerning surveillance and treatment need to be made on case-by-case basis.

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