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CLINICAL NOTE

Cronkhite-Canada syndrome: a new case report of this enigmatic and infrequent disease

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INTRODUCTION

The Cronkhite-Canada syndrome (CCS) is an infrequent disease, non-inherited, characterized by a gastrointestinal non-adenomatous polyposis, chronic diarrhea, low blood proteins, malnutrition and skin and nail alterations (1-6). Etiopathogeny is unknown, there is no effective treatment with a scientific base and, although cases with response to empiric treatments have been described, prognosis is usually poor. We do not know if with an early diagnosis, the prognosis could be better. We expose a new case of this enigmatic and infrequent disease, with no medical treatment response, in order to remind it, improving the casuistry and the available information about it, and promoting, with a higher knowledge and diffusion, an earlier treatment.

CASE REPORT

An 80 year-old-man was admitted to hospital complaining of one month-history of weight loss, abdominal pain and diarrhea. *Family history:* father and eight siblings dead without previous digestive pathology. *Personal history:* no allergies, smoking (60 cigarettes/day) and ethylic (80 g/day) habit until 25 years ago, appendectomy, high blood pressure, emphysematous chronic obstructive pulmonary disease, benign prostatic hypertrophy and generalized osteoarthritis. He was diagnosed 3 years ago of colonic diverticular disease with barium enemas because of hypogastric pain. Colonoscopy study was not realized and blood analysis did not show any significant alteration. At this moment, total blood proteins level was completely normal. Home treatment with tamsulosine, zolpidem tartrate, biotine, candesartan and inhalated formoterol fulmarate, ipratropium bromide and budesonide. He did not normally consume non-steroids anti inflammatory drugs or antibiotics. In the last month, because of the presence of diarrhea, he was treated with loperamide and ciprofloxacin with no response.

—*History of presenting complaint:* over a period of one month, he progressively presented: asthenia, anorexia, weight loss (10 kg), numerous stools preceded by hypogastric pain, with night and day rhythm, soft or liquid consistence, without blood containing but plenty of mucus. He did not refer fever, vomiting or any other interesting symptoms.

—*Physical examination:* physical worsening attributed to advanced age and muscle mass loss. Height 164 cm. Weight 67 kg. He needed help for wandering. Absence of jaundice or skin and mucosal paleness. Presence of hyperpigmented maculas in upper limbs. Poor body hair. No peripheral adenopathies. Normal heart auscultation. Heart frequency: 80 heartbeats per minute. Blood pressure: 150/90 mmHg. *Respiratory auscultation:* diffuse decrease of breath vesicular sounds with poor rhonchus and sibilants. Normal abdominal auscultation with painful palpation in hypogastric region and both iliac fossas, without any mass or visceromegaly. Muscle atrophy in limbs, normal peripheral pulse and absence of edemas.

—*Blood test:* hematocrit values, hemoglobine, mean corpuscular volumen, platelets, glucose, urea, sodium, creatinine, bilirrubine, transaminases, alcaline phosphatase, cholesterol, triglycerides, folic acid, ferritine and B12 vitamin were steady in a normality range. Progres-

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sive elevation in leukocytes values (13,900-30,900, normal 4,600-10,200/mm^3), with neutrocytophilia (70-90%), and reactive C protein (16.9-93.4, normal 0-5 mg/L); decrease in total proteins values (4.4-5.3, normal 6.6-8.7 g/dl), calcium (4.7-7.0, normal 8.5-10.5 mg/dl) and cholinesterase (1,557-2,591, normal 5,300-12,900 U/L). Normal coagulation assay. Proteinogram: hypoalbuminemia (2.49, normal 4.0-4.7 g/dl) and hypogammaglobulinemia (0.39, normal 0.80-1.35 g/dl), with total proteins 4.7 g/dl. Potassium values, which were anodynes over the first weeks of admission, reached values of 2.3-1.9, normal 3.5-5 mEq/L). Increased values of gastrin (263, normal 13-115 pg/ml) and thyrotropin (TSH) (33.9-17.3, normal 0.12-5 uU/ml), decreased thyroxine (T4) (0.56-0.27, normal 0.8-1.8 ng/dl) and normality of serum cortisol. TSH y T4 values were normal at admission. Thyroid anti-peroxidase, anti-tiroglobulin, antinuclear and anti-transglutaminase antibodies were negatives. Normal urinary sediment. Elevation in carcinoembryonic antigen (28.5-88.1, normal 0-5 ng/ml) and CA 19.9 antigen (57.8, normal 0-37 U/ml) values; specific prostatic antigen, alfa-fetoprotein and CA 125 antigen values were normal. Fats quantification in stool tests was invaluable. Microbiology: negativity in stool cultures, urine cultures, parasites in stools, *Clostridium difficile* toxine, mantoux, *Helicobacter pylori* serology, HIV, citomegalovirus, *Salmonella* and enterocolitic *Yersinia*.

—*Ancillary tests:*

• *Colonoscopy* (practiced twice): shows with a diffusive distribution, mainly from rectosigmoid union up to ileocecal valve, multiple nodular or sessile polypoid lesions, with variable sizes, reaching the total occupation of the colon light in some zones, making difficult the endoscopy pass. Lesions show erythematous surface with petechial and ecchymotic lesions. We obtained biopsies from different levels and, in a second-time exploration, a rectal macrobiopsy with polypectomy loop.

• *Gastroscopy:* esophagus, gastric fundus and body were normal. Antral mucosa, mainly prepyloric, and duodenal mucosa showed small nodes with a diffuse distribution.

• *Thorax radiology:* emphysematous blebs in right lung base. No presence of pleural effusion. Suspicion about the presence of pericardial effusion.

• *Bariumize radiology of esophagus, stomach and small bowel:* antral gastric folds were bigger, irregulars and with rounded filling defects. Small bowel folds were as well increased, with a nodular pattern, mainly in jejunum, and contrast dilution.

• *Contrast enema:* diverticulums in sigmoid and left colon. Multiple filling defects throughout the colon.

• *Abdominal computerized tomography:* cysts in left kidney. Probable right suprarenal adenoma. Diverticulums in left and sigmoid colon. Diffuse enlargement of colonic wall. Prostate hypertrophy.

• *Thyroid echography:* normal size of thyroid. Small cysts in right lobe. Left lobe with homogeny and normal echogenicity.

• *Transthoracic echocardiogram:* no images of pericardial effusion, systolic function conserved, mitral and aortic valve insufficiency.

• *Colon biopsies and rectal macrobiopsy histology:* severe distortion in glandular architecture of mucosa, microcystic dilatations and mucin's collections, edematous lamina propria with moderate to severe inflammatory infiltration with numerous plasmatic cells, neutrophilles and eosinophilles. These alterations detected are compatible with the existence of colon and rectum hamartomas.

• *Gastric and duodenal biopsies histology:* we observed glands dilatation with severe mixed inflammatory infiltration, becoming the diagnosis of gastric and duodenal hamartomas.

—*Clinical evolution:* the patient is diagnosed of Cronkhite-Canada syndrome, dying after two months of hospital admission without detecting any clear improvement of the initial clinic profile. He kept up the asthenia and anorexia status, with a variable number of stools plenty of mucous content, increasing the weight loss, and persistent hypoproteinemia with edema in lower limbs. He presented fever (38 ºC) some days with positive blood cultures to *E. coli* related to phlebitis and urinary infections, a tetany episode, pain in lower limbs with a probable neuropathic origin and nail lesions with obvious onycholysis. It is important to stand out the development of hypothyroidism and the elevation of carcinoembryonic antigen. The patient dies after 24 hours of cough with cruentum sputum, dyspnea, respiratory insufficiency data in arterial gasometry and a left base pneumonia in thorax radiology. A necropsy was realized.

—*Treatments:* the patient, over his prolonged hospital dwelling, received treatment, not simultaneously, with: enteral nutrition, oral and by nasogastric tube, fluidotherapy with supplementary potassium chloride, oral and systemic calcium, intravenous albumin omeprazole 20 mg/day, mesalazine, vitamin complex, loratadine 10 mg/day, oral an systemic corticoids subcutaneous octeotride 50 mcg/8 h, gabapentin 300 mg/8 h, antibiotics (piperacillin-tazobactam, amoxicillin-clavulanic, metronidazole and ciprofloxacin), levothyroxine and medical treatment of his previous basal pathology: high blood pressure, chronic bronchopathy and prostate hypertrophy.

—*Necropsy report:* post-mortem examination discoveries coincided with the diagnosis of Cronkhite-Canada syndrome.

—*External examination:* body hair decrease and dark brown macular lesions in upper limbs, especially in the back of the right hand and front side of left forearm. Both hand fingers presented onycholysis with white-yellowed nail pigmentation (Figs. 1 and 2). Bilateral hydrocele. Lower limbs edema.

—*Internal examination:* pericardial and peritoneal effusions. Thyroid hypotrophy. Pulmonary emphysema and left lung pneumonia. Bilateral nodular adrenal hyperplasia. Moderate arterioesclerosis. Prostate adenocarcinoma localized in both lobes without extracapsular or metastatic affec-

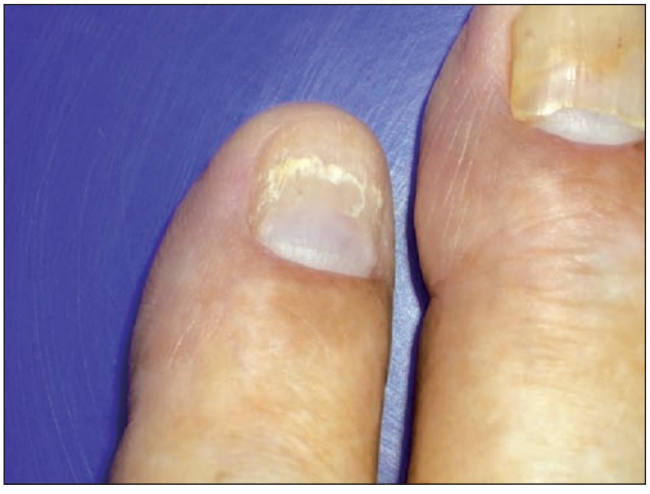


Fig. 1. Onycholysis with white - yellowed thumbnail discoloration.
Onicólisis con decoloración ungueal blanquecino-amarillenta.

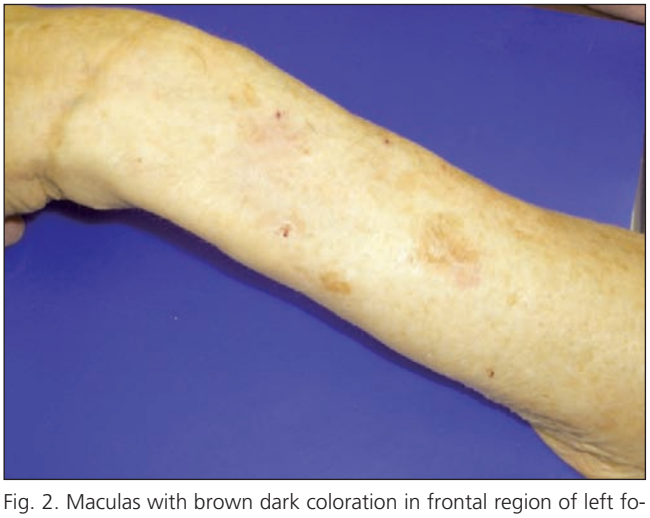


Fig. 2. Maculas with brown dark coloration in frontal region of left forearm.
Máculas de coloración pardo-oscuras en región anterior de antebrazo izquierdo.

tation. Testicular atrophy. There were no notable changes in liver, biliary tract or pancreas. Digestive tract study: esophagus without any abnormality. Gastric body showed a decrease of the folds. Gastric antrum showed a wrinkled surface, "studded-like", with a nodular increase of the folds and superficial ecchymosis (Fig. 3), keeping these changes up to second duodenal portion, where is more evident the presence of sessile polyps. In jejunum and ileum there was not any significant disorder. Colonic mucosa showed, in its whole extension, polypoid morphology, with multiple sessile prominences, with ecchymotic surface and friable appearance. These alterations are less obvious in right colon. Existence of diverticulums in left colon.

Microscopically it was striking the antrum, duodenum, colon and rectum affectation (in their entirety), showing similar histopathology, with the presence of multiple poly-

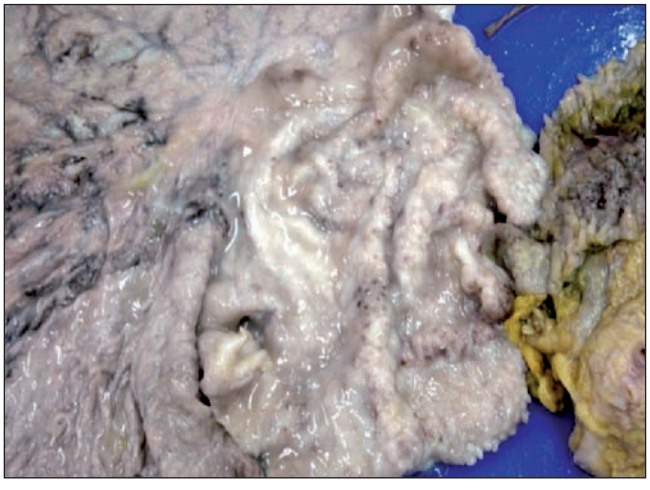


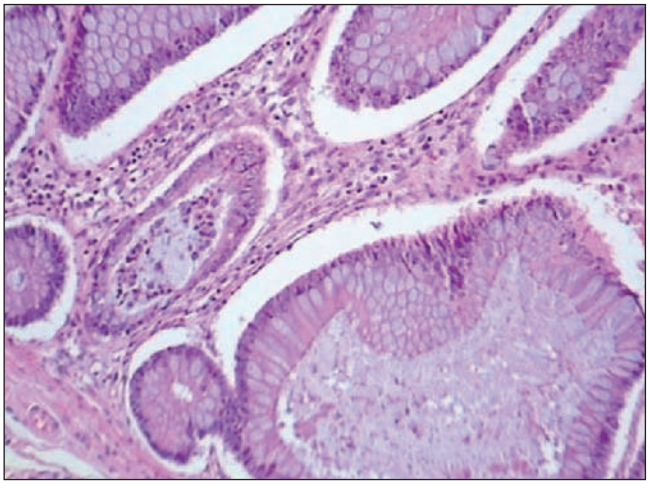
Fig. 3. Gastric mucosa with polypoid morphology, with multiple sessile prominences and ecchymotic surface.
Mucosa gástrica con morfología polipoidea, con múltiples prominencias sésiles y de superficie equimótica.

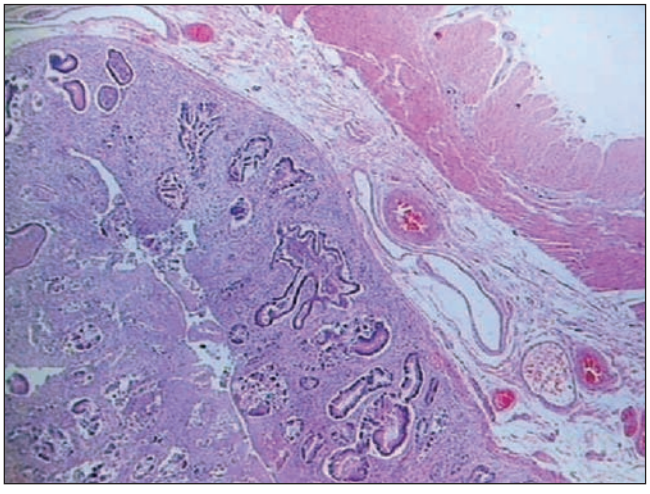
poid formations, some of them hamartomatous, with enlarged and cystic crypts, decreased in number and with mucus hypersecretion. In lamina propria we observed edema with muscularis mucosa fibers hyperplasia, and chronic low-moderated inflammation (Figs. 4 and 5). There is a reduction of intestinal villi in duodenum and colon, and a gastric fundus and body folds decrease. We did not recognize any dysplasia sign in any of the observed cuts.

Death cause: severe malnutrition due to Cronkhite Canada syndrome. Left lung pneumonia.

DISCUSSION

The Cronkhite Canada syndrome (CCS) was described for first time in 1955, and it is characterized by a clinical picture of chronic diarrhea with hypoproteinemia and malnutrition, alopecia, skin pigmentation and onychodystrophy (1-6). In stomach, small bowel and colon, but not in esophagus, multiple hamartomatous polyps are detected. They are sessile polyps with superficial erosions. At microscopy show lamina propria edema and cystic glandular enlargement with accumulation of mucinous material, polymorphonuclear aggregates and lymphoplasmacytic and eosinophilic inflammatory infiltrates (1,2,5-10). In some cases it has been described the existence of an outstanding mast cells infiltrate (1,2,6). Skin pigmentation shaped like brown macular lesions because of the accumulation of melanin in basal layer, use to be demonstrated in limbs, palms, plants, face and neck (1-6,11). Nails show dystrophic changes and, in advanced cases, easily detached themselves from nail bed. CCS is included in the differential diagnosis of the gastrointestinal polyposis, non adenomatous and non inherited, as lym-





Figs. 4 and 5. Histological cuts evidence polypoid formations, most of them hamartomatous, with enlarged and cystic crypts with mucus hypersecretion. Edema with muscularis mucosa fibers hyperplasia. We did not detect any justification to carcinoembryonic antigen increased values.
Cortes histológicos que evidencian formaciones polipoides, la mayoría hamartomatosas, de criptas dilatadas y quísticas con hipersecreción mucosa. Edema con hiperplasia de las fibras de la muscularis mucosa. No se detectó justificación para la elevación de las cifras de antígeno carcinoembrionario.

phoid nodular hyperplasia and hyperplasic, inflammatory, lipomatous or lymphomatous polyposis (1-3,8,12-16). It is a very infrequent disease, at least in occidental countries, leading most of published cases to Asiatic countries. In Spain we have just two reference of reported cases (2,3), while in Japan there have been published reviews with over one hundred cases. Etiopathology of CCS is still unknown (2,4,14). Histological data and the occasional response to treatments with antibiotics or corticoids, guide us to a disease with an inflammatory base that could be influenced in some way by bacterial agents (1,2,8,11). Recently it has been published a possible relation to the *Helicobacter pylori* infection (17). It is a disease with poor prognosis (1,2,11,16,18). Most of patients with CCS die because of a severe malnutrition picture, frequently complicated with infections (1,2,5,9,10). It has been described remissions of the disease after improving nutritional status and restoring the electrolytes disorders of these patients (1,2,6,8-11), as well as using the association of drugs like antibiotics (ampicillin, tetracyclines, metronidazole, ciprofloxacin, etc.) (1,7), oral and intravenous corticoids (1,2,6,8-11), H1 and H2 receptor antagonists of histamine (loratadine and ranitidine) (8), antidiarrheal drugs or disodium cromoglycate. There is no doubt about the need of nutritional treatment, oral or parenteral, as well as the control of ionic and trace elements deficiency. The mentioned pharmacological treatment, in the other hand, is totally empiric, with no scientific evidence, and its results are completely unpredictable. There is the possibility, especially in cases with localized and not very extended affection, of extirpating the intestinal segment affected. It has been reported one case of improvement after hemicolectomy (1,2,10).

CCS is not considered a gastrointestinal premalignant disease, however is remarkable a relatively frequent communication of patients with colonic adenocarcinoma or with adenomatous changes in these hamartomatous polyps (1,6,7,12,13).

Our patient presented the typical medical picture of CCS without improvement despite medical treatment similar to those described by other authors with better results, dying in a situation of malnutrition, respiratory insufficiency and sepsis related to pneumonia. We stand out, like other published case reports (11,19,20), the development of hypothyroidism, initially related to malnutrition and, on the other hand, the increase of CEA without detecting in the practiced studies, including necropsy, dates of digestive neoplasm, beyond the prostate neoplasm.

The infrequency of CCS and the numerous doubts aroused, especially about etiopathogenesis and treatment, motive the divulgation of clinical reports of this disease in order to remind it, improve knowledge of it increasing casuistry and promoting earlier diagnosis, previous to the instauration of severe malnutrition, and trying to improve the prognosis.

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