

Manuscript Review

Dear Editor and reviewers, thanks for considering and reviewing our manuscript, and thanks for your valuable comments.

This is a point to point response to your comments; we are hoping that it will satisfy your valuable queries and comments, thanks.

- A. The author described a female patient with Cronkhite-Canada syndrome and made many efforts for the differential diagnosis about the rare case. Some comments for this manuscript :

1. It is not the first CCS patient from Middle East at least. Please see Case Rep Gastroenterol. 2018 Apr 13;12(1):109-115.

Answer: Thanks for your comment. We have modified it as for our knowledge, it is the the 1st case reported from Egypt and North Africa, but not from the whole Middle East, since few cases of Cronkhite-Canada syndrome were reported from Iran.

2.The figure of colonoscopy is not typical, and please use a typical image in the patient.

Answer: Thanks for your comment. We have modified the figure of colonoscopy.

3.Except the first case in Egypt, is there any novel finding in this case?

Answer: Thanks for your comment. It is a very rare case and despite its rarity, it should be one of the differential diagnoses for any gastrointestinal polyposis. Also, there is a tendency of malignant transformation or coexistence of gastrointestinal malignancies in patients with Cronkhite-Canada syndrome. So, it is important to raise the awareness for this syndrome.

4. There are some advances in the pathogenesis and prognosis of CCS, which will help to make decision for the future medications of this case.

Answer: Thanks for your comment. We have modified some points in the manuscript regarding the advances in the pathogenesis and prognosis of CCS.

5. Did the patient have pigmentation of skin or any abnormality of taste?

Answer: Thanks for your comment. Our case had no skin pigmentation or any abnormality of taste.

6. The EUS image could be deleted.

Answer: Thanks for your comment. Endoscopic ultrasound (EUS) was done and showed significantly hypertrophic mucosa, muscularis mucosa, while the submucosa and the muscularis propria are spared favoring its benign nature. So, Lymphoma and other GI malignancies were excluded due to sparing the muscularis propria.

7. An image showing the improvement after medication is suggested.

Answer: Thanks for your comment. We added follow-up endoscopies after 6 and 12 months of treatment.

B. Alzamzam, et al presented the first case of CCS in Egypt. I am wondering if the diagnosis is correct or not. Therefore, authors should discuss it in discussion. Polypoid lesions in both stomach and colon are unlikely for CCS. Especially, the figure 4 (colon polyp) should be changed the figure that showed polypoid lesions. Authors should show the endoscopy which show the improvement by the treatment.

Answer: Thanks for your comment. Polypoid lesions in both stomach and colon are not that unlikely for CCS as published in many literatures such as Dharmik P, Mani TM (2018) A case with rare manifestation of Cronkhite-Canada Syndrome with remission after treatment and literature review. Glob J Medical Clin Case Rep 5(4): 025-029. DOI: <http://doi.org/10.17352/2455-5282.000065>, and Itzkowitz SH, Potack

**J. Colonic polyps and polyposis syndrome. Sleisenger and Fordtrans
Gastrointestinal and Liver Disease (10th Edn.). Elsevier Philadelphia, Pa, USA 2015.
We have modified some points in the manuscript according to your valuable
comments. We have modified the figure of colonoscopy and added follow up figures.**

Cronkhite-Canada syndrome: First case report from Egypt and North Africa

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Abstract:

A 60-year-old female patient presented with dyspepsia, abdominal pain, and weight loss of one-year duration. Her physical examination showed alopecia and onychodystrophy. Upper endoscopy revealed diffuse markedly thickened gastric mucosa involving the whole stomach with thickened gastric rugae and numerous polypoidal lesions. Histopathological examination showed marked hyperplasia of the foveolar glands with inflammatory cell infiltration. EUS showed significantly hypertrophic mucosa, muscularis mucosa, while the submucosa and the muscularis propria are spared favoring its benign nature. Colonoscopy showed multiple sessile polyps scattered at different parts of the colon. Histopathological examination revealed tubular adenomatous polyps with low-grade dysplasia. Differential diagnoses included: Cronkhite-Canada syndrome (CCS), Menterier disease (MD), other polyposis syndromes, lymphoma, amyloidosis, and gastric malignancies. The presence of alopecia, nail dystrophy, gastrointestinal polyposis, markedly thickened gastric mucosa and folds, abdominal pain, weight loss, and marked foveolar gland hyperplasia, all were in favor of CCS. Lymphoma was excluded due to sparing the muscularis propria. The presence of colonic polyps, antral and duodenal infiltration, and the absence of hypoproteinaemia decrease the possibility for MD.

Introduction:

Cronkhite-Canada syndrome (CCS) is one of the rarest nonhereditary diseases¹ that its exact aetiology is still unknown;² with only 500 cases have been described in the literature.³ Most of CCS were reported from Japan, and for our knowledge, our case is the 1st case reported from Egypt and North Africa.

Patient with CCS usually presents with gastrointestinal (GI) symptoms such as abdominal pain, weight loss, and diarrhea, or with other symptoms such as onychodystrophy, alopecia, hyperpigmentation of the skin, and rarely vitiligo.⁴

Gastrointestinal polyposis is the main endoscopic feature in CCS, which is commonly non-neoplastic and rather inflammatory, hyperplastic, hamartomatous, and/or adenomatous polyps in nature.⁵ Moreover, some CCS cases may develop gastric and colorectal malignancies during the disease course.⁴

Case presentation:

A 60-year-old female patient presented with dyspepsia, abdominal pain, and weight loss of one-year duration. She denied other GI or anaemic symptoms. She was non-smoker and did not drink alcohol. There was no family history of gastrointestinal polyposis or colorectal malignancy. Her past medical history was free apart from prolonged Proton-pump inhibitor (PPI) intake. Her physical examination was unremarkable apart from alopecia (figure 1) and onychodystrophy (figure 2). Her laboratory profile was within normal limits including a full complete blood picture (CBC), chemistry, serum albumin, serum calcium, urine analysis, antinuclear antibody (ANA), and IgG-4.

Oesophago-gastro-duodenoscopy (OGD) revealed diffuse markedly thickened gastric mucosa involving the whole stomach (fundus, body, and antrum), with thickened and tortuous gastric

rugae, and numerous polypoidal lesions (3-10 mm in diameter), with hyperaemic mucosa, and to lesser extent down to the duodenal bulb and second part of the duodenum (figure 3). Multiple conventional biopsies were taken, and polypectomy was done for the large polyps for histopathological examination. Biopsies showed marked hyperplasia and cystic dilation of foveolar glands with inflammatory cell infiltration including eosinophils, hyperplastic polyps, chronic gastritis, and *Helicobacter pylori* (*H. pylori*) association with no atypia or malignancy (figure 6). IgG4-immunohistochemistry showed a very faintly positive signal.

Endoscopic ultrasound (EUS) was done later and showed significantly hypertrophic mucosa, muscularis mucosa, while the submucosa and the muscularis propria are spared favoring its benign nature. Wall thickness is up to 8-10 mm (Normal is up to 4 mm) (figure 4).

Colonoscopy showed multiple variable-sized, sessile, and pedunculated polyps, about 15 polyps, scattered at different parts of the colon, snaring of the large polyps was done after submucosal injection (figure 5), histopathological examination showed typical features of benign juvenile-like and hamartomatous polyps without dysplastic changes, while other polyps pathology revealed tubular adenomatous polyps with low-grade dysplasia.

Both push enteroscopy and terminal ileoscopy showed no polyposis with normal mucosa in the 3rd and 4th portions of the duodenum, the proximal jejunum, and the terminal ileum.

Computerized tomography (CT) scan of the abdomen & pelvis with contrast revealed mild circumferential mural thickening of the gastric wall.

Discussion:

In our case, the following differential diagnoses were raised and discussed with our gastroenterologists: Cronkhite–Canada Syndrome (CCS), Menterier disease (MD), other polyposis syndromes (such as familial adenomatous polyposis, Gardner syndrome, juvenile polyposis, Peutz-Jeghers syndrome and Turcot syndrome), lymphoma, amyloidosis, duodenal gastric heterotopia, and gastric malignancies.

The diagnosis was based on history, physical examination, endoscopic findings, and histology. The presence of anomalies of ectodermal tissues (such as alopecia and nail dystrophy), gastrointestinal polyposis (hamartomatous and adenomatous polyps), markedly thickened gastric mucosa and folds, abdominal pain, weight loss and marked foveolar gland hyperplasia, all were in favor of the Cronkhite–Canada syndrome. On the other hand, there was no protein-losing enteropathy, diarrhea, hypoalbuminaemia or skin pigmentation.

Lymphoma was excluded due to sparing the muscularis propria. Furthermore, markedly thickened gastric mucosa and folds and the histopathological examination which revealed marked foveolar gland hyperplasia were consistent with Menterier's disease. In addition, abdominal pain and weight loss are a common presentation of Menterier's disease, but the presence of colonic polyps, antral and duodenal infiltration, and the absence of hypoproteinaemia decrease the possibility for MD.

The patient started a sequential therapy for *H pylori* infection with complete eradication, followed by proton pump inhibitors (40 mg once daily), prednisolone (30 mg/day), and mesalazine (500 mg QID) for 6 months.

Common complications of CCS include anemia, intussusception, rectal prolapse, and gastrointestinal bleeding, other less common as recurrent severe acute pancreatitis, myelodysplastic

syndrome, cecal intussusception, portal thrombosis, membranous glomerulonephritis and osteoporotic fractures that may result from malabsorption of calcium or prolonged glucocorticoid therapy or both. The most serious complication is malignancy; however, the incidence of CCS-related cancer is estimated to be 5–25%, especially gastric and colon cancer.⁶

The follow-up endoscopies (OGD and colonoscopy) after six and twelve months of treatment showed significant remission with a reduced number of gastric and colonic polyps and regression of hypertrophic gastric folds (figure 7). Consequently, the patient's clinical condition was markedly improved, and the prednisolone dose was reduced gradually to 7.5 mg/d, but the mesalazine dose remained the same.

There is a tendency of malignant transformation or coexistence of gastrointestinal malignancies in patients with CCS. So, Endoscopic documentation of regression in CCS is important despite the lower incidence of CCS-related cancer in remission patients. Therefore, the comprehensive endoscopic annual surveillance either via chromoendoscopy or directed biopsy from irregular polyps, to exclude pre-cancer lesions before development of invasive carcinoma is mandatory, however there are still no recommended guidelines to be followed.⁷

Nutritional support, electrolytes, mineral and vitamin supplementation remains the cornerstone in treatment of CCS beside antibiotics, and corticosteroids, however the definitive treatment is still unknown.⁷⁸

Till now, there is still much that needed to know about this syndrome. In this context, the most important issue is to maintain treatment monitoring and provide appropriate measure to prevent relapse.⁹

Conclusion:

Cronkhite-Canada syndrome (CCS) is one of the rarest nonhereditary diseases that its exact aetiology is still unknown; with only 500 cases have been described in the literature. Most of CCS were reported from Japan, and for our knowledge, our case is the 1st case reported from Egypt and North Africa.

Keywords: Cronkhite-Canada syndrome, Gastrointestinal polyposis, Menetrier disease, Thickened gastric mucosa, and folds.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Legends of figures:

Figure 1: Alopecia



Figure 2: Onychodystrophy



Figure 3: Upper endoscopy

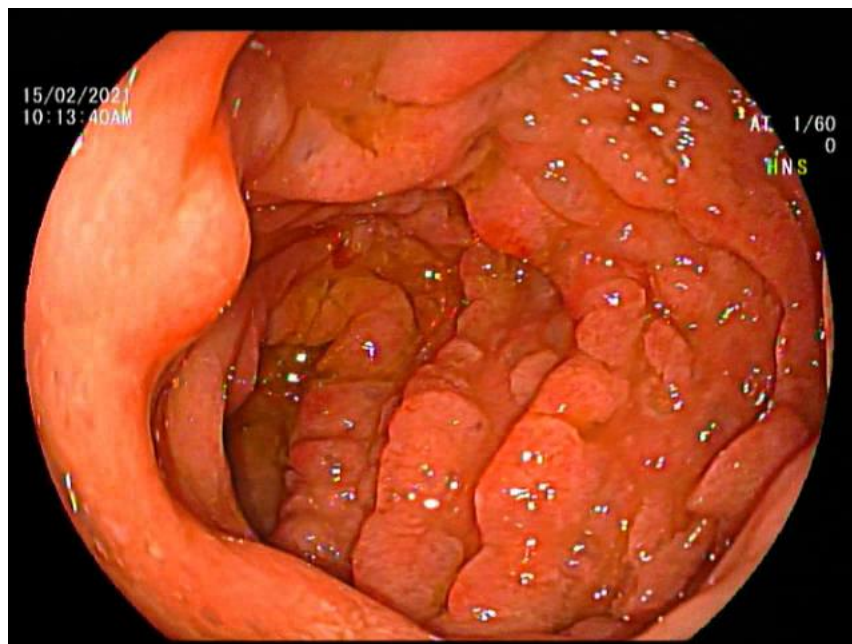
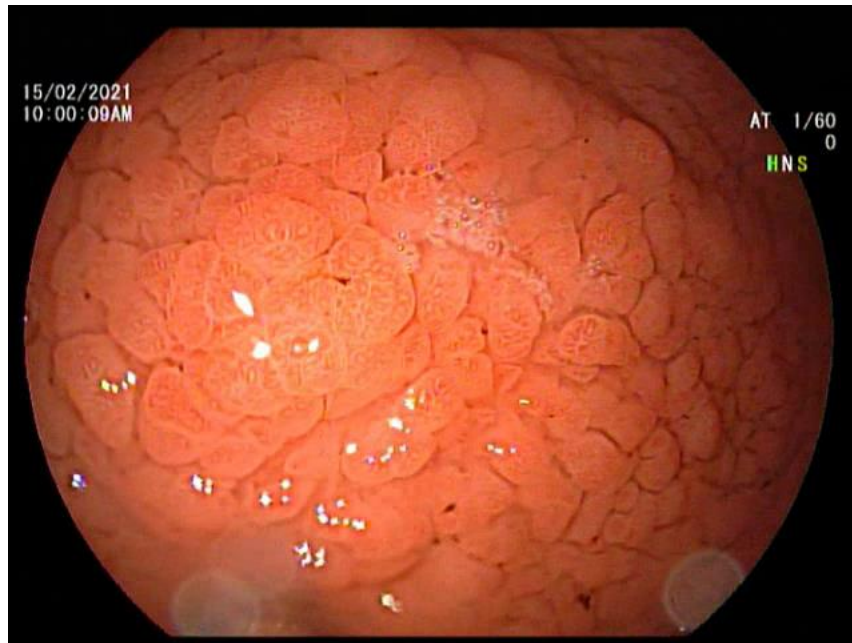


Figure 4: EUS



Figure 5: Colonoscopy

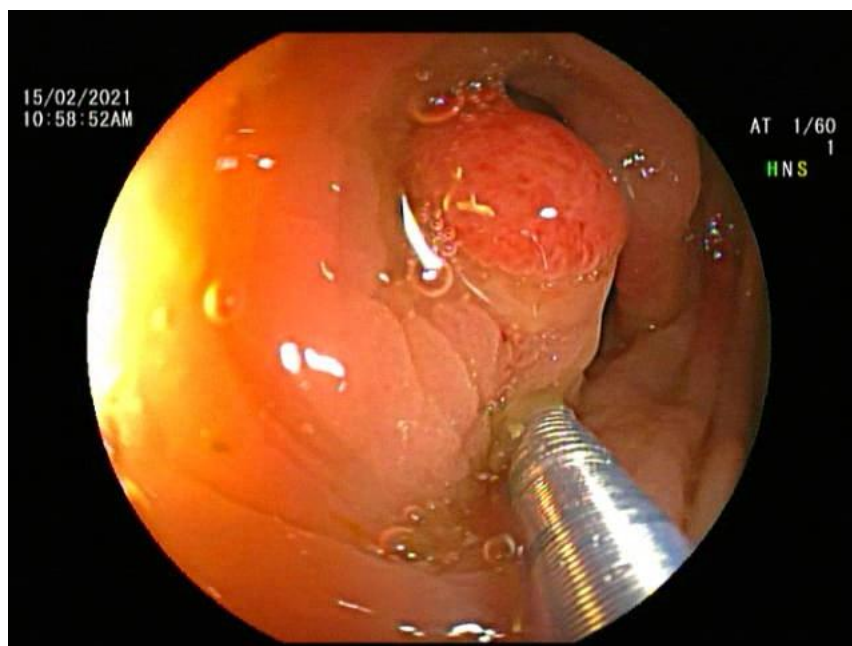
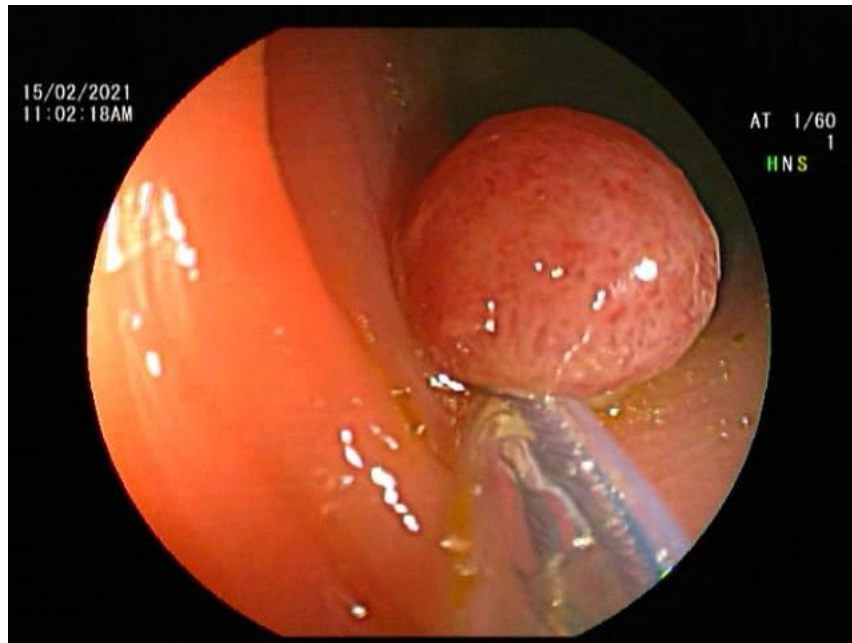


Figure 6: Histopathological examination

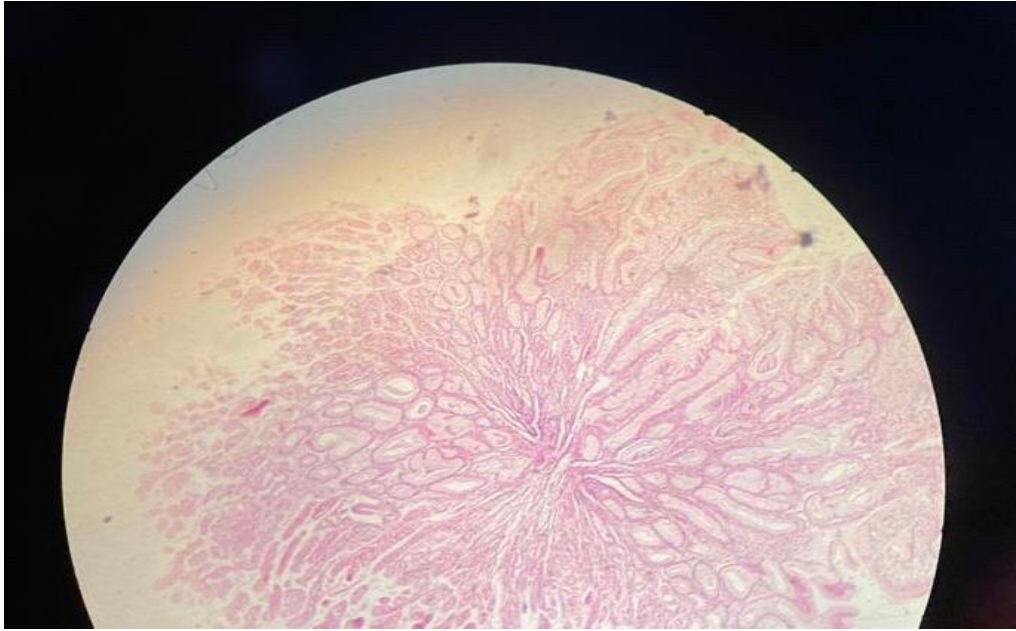
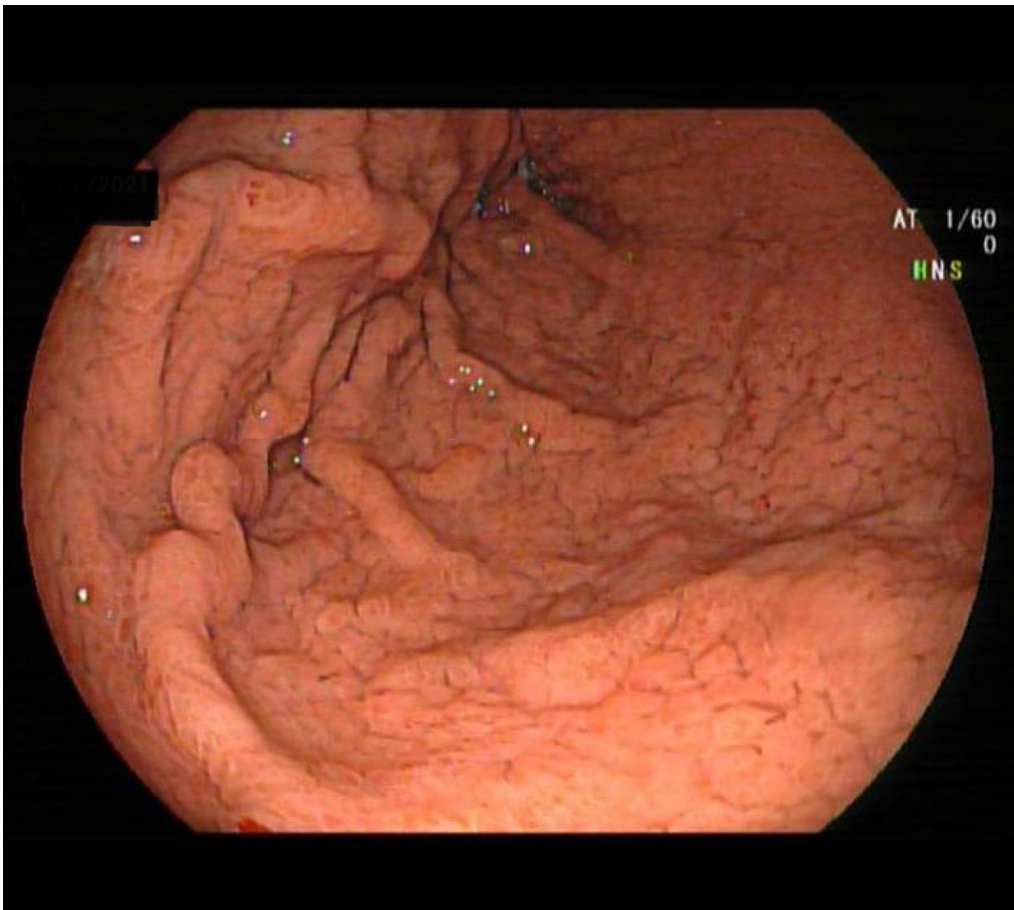


Figure 7: Follow-up endoscopies after 6 and 12 months of treatment; (A) Upper endoscopy, (B) Colonoscopy.



(A) Upper endoscopy.



(B) Colonoscopy.