To the Editors,

Protein-losing gastroenteropathy should be considered in patients presenting with hypoalbuminemia who have normal nutritional status, kidney and liver function. Identifying the underlying cause of protein-losing enteropathy is required to provide adequate treatment.

Case Report

A 69-year-old man with Indian parents living in the Netherlands since 1975 was referred to our tertiary center with progressive complaints of upper abdominal pain, progressive diarrhea, and 11 kg of weight gain in 2 weeks. His medical history included sarcoidosis, psoriasis, and type 2 diabetes, among others. On physical examination he was alert and had normal vital signs. Severe peripheral edema, hyperpigmentation, alopecia, and dystrophy of his nails were observed (Figure 1A-C). His pruritus, attributed to iron deficiency during dermatology consultation 3 months earlier, persisted. Palpitation of the abdomen was painful without signs of rebound tenderness. Blood tests showed microcytic anemia (Hb 12.3 g/dL, MCV 75,8), hypoalbuminemia with progressive complaints of upper abdominal pain, progressive diarrhea, and 11 kg of weight gain in 2 weeks. His medical history included sarcoidosis, psoriasis, and type 2 diabetes, among others. On physical examination he was alert and had normal vital signs. Severe peripheral edema, hyperpigmentation, alopecia, and dystrophy of his nails were observed (Figure 1A-C). His pruritus, attributed to iron deficiency during dermatology consultation 3 months earlier, persisted. Palpitation of the abdomen was painful without signs of rebound tenderness. Blood tests showed microcytic anemia (Hb 12.3 g/dL, MCV 75,8), hypoalbuminemia

Figure 1. This 69-year-old patient presenting with progressive diarrhea for 2 weeks showed ectopic changes that originated at the same time (A-C). Esophagogastroduodenoscopy (D) and colonoscopy (E) showed substantial abnormalities in the entire stomach, duodenum, and colon, including edematous mucosa with giant gastric folds and erythematous polyps.
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(20 g/L), a decreased corrected calcium (1.44 mmol/L), hypophosphatemia (0.32 mmol/L), and hypomagnesemia (0.47 mmol/L). Elevated fecal alpha-1 antitrypsin clearance was observed (400 mg/dL). White blood cell count, C-reactive protein, and kidney and liver function were normal. No proteinuria was observed. Fecal and blood cultures remained negative.

On esophagogastroduodenoscopy, the stomach and duodenum showed striking abnormalities such as an edematous mucosa with giant gastric folds and erythematous sessile polyps; the esophagus was normal (Figure 1D). Colonoscopy and capsule endoscopy revealed a continuation of this pattern including edematous mucosa with numerous sessile polyps (Figure 1E). Multiple biopsies were taken, and 1 polyp was removed for histopathological analysis. Pathology of duodenal and colon biopsies showed hamartomatous polyps with hyperplastic epithelium, stromal inflammation, and edema (Figure 2A). Additional IgG4-immunohistochemistry showed regions of strong staining in plasma cells. This combination of clinical, endoscopic, and histopathological findings confirmed our diagnosis of the Cronkhite-Canada syndrome.

Treatment was started with 60 mg of intravenous prednisolone; and intravenous supplementation of calcium, phosphate, and magnesium started. Nutritional status was optimized with total parental nutrition. The patient showed clinical improvement with stool frequency decreasing from 10 times a day to 1-2 times a day. Abdominal pain disappeared and peripheral edema was significantly reduced. Gradually, head hair and facial hair returned (Figure 2B).

Discussion

Protein-losing enteropathy is manifestation that can be caused by multiple groups of disorders. Generally, these disorders can be divided into erosive gastrointestinal diseases, nonerosive gastrointestinal diseases, and diseases that cause lymphatic obstruction or altered lymph flow. The differential diagnosis of this case (ie, nonerosive mucosa with polyposis and hyperplastic gastric folds) includes a number of diseases, such as Menetrier’s disease, familial adenomatous polyposis, and Peutz-Jeghers syndrome. In this case, Cronkhite-Canada syndrome was considered early in the diagnostic workup due to the medical history characterized by multiple autoimmune diseases. The remarkable protein-losing enteropathy, in combination with the presentation of skin hyperpigmentation, alopecia and nail dystrophy, raised the clinical suspicion of Cronkhite-Canada syndrome, which was later on confirmed by endoscopic and histopathological findings.

Cronkhite-Canada syndrome is a very rare (incidence of 3 per 1,000,000) nonhereditary syndrome and can cause protein-losing enteropathy—this can only be diagnosed after exclusion of liver or kidney failure and malnutrition—and is typically accompanied with ectopic changes.1 Typical clinical features include protein-losing enteropathy, alopecia, nail dystrophy, and hyperpigmentation. Gastrointestinal endoscopy is characterized by diffuse mucosal edema of the entire gastrointestinal tract with generalized polyposis and normal esophagus. Although the etiology and pathogenesis of Cronkhite-Canada syndrome remain unclear, the consensus is an autoimmune disease. This hypothesis is supported by the co-occurrence of other autoimmune diseases, elevated IgG4 in both serum levels and immunohistochemistry, and response to steroids.1,2 Intravenous corticosteroid treatment is recommended as the main treatment together with nutritional support. The limited available literature suggests thiopurines and antitumor necrosis factor therapy in case of nonresponse or maintenance therapy.3,4

Acknowledgments

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Conflicts of Interest

The authors declare no conflict of interest

References

1. Sweetser S, Ahlquist DA, Osborn NK, et al. Clinicopathologic features and treatment outcomes in Cronkhite-Canada syndrome: support for autoimmunity. Dig Dis Sci. 2012;57(2):496–502.
2. Zhu LP, Zhong WL, Wang ZG, et al. Cronkhite-Canada syndrome: an investigation in clinical features and pathogenesis. J Dig Dis. 2021;21(11):663–671.
3. 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.
4. Watanabe D, Ooi M, Hoshi N, et al. Successful treatment of Cronkhite-Canada syndrome using anti-tumor necrosis factor antibody therapy. Endoscopy 2014;46(S 01):E476–E477.