Cronkhite–Canada syndrome: report of a rare case and review of the literature

Yuping Liu¹*, Li Zhang¹*, Yingshan Yang² and Tao Peng³

Abstract
Cronkhite–Canada syndrome is rarely encountered in clinical practice. Notably, most patients with Cronkhite–Canada syndrome exhibit hypoalbuminemia. Because the cause of Cronkhite–Canada syndrome is unknown, no specific treatment method has been established. Here, we describe a 59-year-old woman with Cronkhite–Canada syndrome in whom clinical manifestations were considerably relieved after treatment with prednisone.

Keywords
Cronkhite–Canada syndrome, prednisone, hypoalbuminemia, intestinal polyposis, blood protein disorders, metabolic diseases

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Introduction
Cronkhite–Canada syndrome is a disease involving multiple gastrointestinal polyps and other manifestations.¹,² Most patients exhibit hypoalbuminemia (<30 g/L) with reduced total serum protein (<60 g/L).³ The disease was first reported in 1955,⁴ and was named Cronkhite–Canada syndrome by Jarnum and Jensen in 1966;⁵ however, the etiology and cause have remained unclear thus far. Therefore, specific treatment methods have not yet been established. The prognosis of patients with
Cronkhite–Canada syndrome remains poor, with a 5-year mortality rate of 55%. Here, we describe a 59-year-old woman with Cronkhite–Canada syndrome who had multiple gastrointestinal polyps and severe hypoalbuminemia over a 98-month course of disease. Notably, she required recurrent and prolonged hospitalization related to hypoalbuminemia. After treatment with glucocorticoid, she experienced substantial relief of disease manifestations.

**Case report**

**Patient history**

A 59-year-old Chinese woman presented with an 8-year history of chronic gastritis, accompanied by frequent nausea and acid reflux, loss of appetite, abnormal taste, and fatigue. She reported a history of upper gastrointestinal endoscopy 6 years prior, which was unsuccessful. She had an 8-month history of edema in both lower extremities, for which she had previously sought treatment at a local hospital. Tests conducted at the local hospital revealed hypoalbuminemia (20.7 g/L) and trace albuminuria (260 mg/L), but the patient refused further treatment.

**Clinical and laboratory findings**

On physical examination after admission to our hospital, the patient exhibited edema in bilateral eyelids and lower limbs without bleeding points, purpura, or oral ulcers. She exhibited pigmentation on her back and partial nail dystrophy, particularly involving the second and fifth toenails of the left foot and big toenail of the right foot (Figure 1). Pertinent laboratory findings included hypoalbuminemia (serum albumin, 21.8 g/L) with reduced total protein (46.6 g/L), as well as anemia (serum iron, 74 g/L). Notably, the level of urinary albumin was high (537 mg/L) and serum cancer antigen (CA) 125 was above normal (415 U/mL). Levels of potassium, calcium, phosphorous, carbon dioxide combining power, erythrocyte sedimentation, C-reactive protein, blood urea nitrogen, serum creatinine, alanine aminotransferase, and aspartate aminotransferase were normal. In addition, levels of coagulation-related indicators, D-dimer, rheumatoid factor, antistreptolysin O, antinuclear antibodies, dsDNA, antineutrophil cytoplasmic antibodies, C3, and C4 were normal. Serum immunofixation electrophoresis, blood/urinary light chain, anti-glomerular basement membrane antibody, anti-phospholipase A2 receptor antibody, and IgG4 findings were also normal.

**Imaging and endoscopic findings**

After admission, the patient underwent upper gastrointestinal barium examination and electronic gastrointestinal endoscopy. Radiographic assessment of the barium examination revealed normal peristalsis and thickening of the gastrointestinal mucosa. Endoscopy revealed a large number of polyps covering the gastric mucosa, as well as multiple mucosal bulges, surface hyperemia and edema, and some erosion. The largest polyp constituted a columnar structure with a length of 1.5 cm (Figure 2). Pathological manifestations of polyps comprised acute/chronic inflammation of the
gastrointestinal tract mucosa, with substantial inflammatory cell infiltration; in particular, eosinophil infiltration and small vessel hyperplasia were observed (Figure 3). Computed tomography examination revealed ascites, pelvic effusion, and a slightly thickened gastrointestinal wall. Because of financial limitations, the patient did not undergo further examination of emission computed tomography and bone density.

**Diagnosis and treatment**

Clinical manifestations, laboratory findings, and imaging results were suggestive of Cronkhite–Canada syndrome. Therefore, treatment was initiated with methylprednisolone 40 mg intravenously three times per day for 3 days; the patient was then switched to prednisone 50 mg/day (1 mg/kg) with other supportive treatment. Notably, tacrolimus, methicillin, azathioprine, and mycophenolate mofetil were all refused by the patient and her family because of their high costs. Prednisone was reduced to 45 mg/day after 2 weeks, then reduced by 5 mg at approximately 2-week intervals; thus, after 5 months of treatment, it was administered at 10 mg/day. After 5 months of treatment, the dose was modified to prednisone 5 mg daily for 3 months; the patient currently is prescribed prednisone 2.5 mg daily. Repeat gastrointestinal endoscopy showed polyp shrinkage. Serum albumin increased to 28.8 g/L after 1 month of treatment, then to 33.1 g/L after 3 months of treatment. At the 3-month follow-up, CA125 had decreased to 46 U/L, hemoglobin had increased to 91 g/L, and serum albumin had increased to 79.6 g/L. Edema disappeared from the patient’s eyelids and lower limbs; nausea and acid reflux, loss of appetite, abnormal taste, and fatigue all gradually resolved during the course of treatment. Furthermore, edema and fullness of the abdomen disappeared. The patient’s appetite gradually improved; after 3 months, she returned to her normal (pre-illness) diet, and gained approximately 4.5 kg in weight.

**Patient consent**

Because this was a retrospective report, we have obtained consent from the patient and her family before publication of relevant data. Additionally, because this was a retrospective report, our group presumed that no registration was necessary; informed consent was obtained from the patient before the study was started.
Discussion

Cronkhite–Canada syndrome is an extremely rare clinical disease with multiple gastrointestinal polyps; 88% of affected patients exhibit hypoalbuminemia. In recent years, the incidence of Cronkhite–Canada syndrome has increased. The age at onset ranges from 26 to 85 years (mean age, 61 years). There is no difference in the incidence of disease between men and women in Europe or the United States. Common predisposing factors are mental stimulation, overwork, or surgery. The present patient was a 59-year-old woman from a rural area with a low socioeconomic status. The patient reported that, when she felt fatigued, her symptoms and edema worsened; they were slightly relieved by rest. Before admission to our hospital, she had experienced fatigue for 4 days.

Gastrointestinal symptoms are the main manifestations, including abdominal pain and diarrhea; these are accompanied by frequent nausea and acid reflux, anorexia, parageusia, or fatigue. Some patients exhibit skin pigmentation on the back, back of hands, and feet; some patients have nail dystrophy, which involves one or more digits. Additionally, some patients have edema, especially in the eyelids and extremities. The present patient had an 8-year history of chronic gastritis with frequent nausea and acid reflux, as well as anorexia. She exhibited edema in bilateral eyelids and lower limbs, as well as pigmentaion on her back and partial nail dystrophy on her toes.

In laboratory tests, more than 88% of patients exhibit hypoalbuminemia (serum albumin, 21.8 g/L); her urinary albumin level was also high (537 mg/L). She exhibited multiple polyps in the gastrointestinal tract (up to 1.5 cm). The CA125 level can be elevated in patients with serous effusion. After treatment, when effusions are reduced or resolved, the CA125 level can be considerably reduced. Our patient exhibited this elevated level of CA125; other diseases were excluded from the differential diagnosis by computed tomography imaging.

Therapy for Cronkhite–Canada syndrome includes glucocorticoid and supportive treatment. Although the effectiveness of glucocorticoid treatment for Cronkhite–Canada syndrome is uncertain, it has become the first empirical treatment. Glucocorticoid dosage is generally considered to be based on body weight (1 mg/kg); its therapeutic mechanism may involve reduction of gastrointestinal inflammation and inhibition of autoimmune responses. In addition to glucocorticoid therapy, supportive treatment is important. Other immunosuppressive agents, such as tacrolimus, have been shown to exhibit partial effects. Our patient accepted glucocorticoid (methylprednisolone and prednisolone) with other supportive treatments; however, the patient and her family refused tacrolimus, methicillin, azathioprine, and mycophenolate mofetil because of their high costs. After treatment, clinical manifestations were considerably ameliorated and all laboratory test indicators showed improvement. The patient’s health gradually returned to normal, such that she did not exhibit nausea, acid reflux, or fatigue.

In conclusion, Cronkhite–Canada syndrome is rarely encountered in clinical practice. It is not difficult to diagnose by use of typical clinical and laboratory tests, but patients’ symptoms may be atypical. For treatment, glucocorticoid is the first drug of choice. Detailed observation and documentation of Cronkhite–Canada syndrome may contribute to an in-depth understanding.
of the mechanism and pathogenesis of the disease, although the specific pathophysiological mechanism remains unknown.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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ORCID iD
Tao Peng https://orcid.org/0000-0002-4300-7806

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