Cronkhite-Canada Syndrome Associated with Schizophrenia

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Abstract

Here, we report a case of Cronkhite-Canada syndrome in a patient with schizophrenia. A 64-year-old man, who had been diagnosed as having a schizophrenic disorder at the age of 30, presented with alopecia, atrophic nail changes, hyperpigmentation of the skin, and inflammatory polyposis of the stomach and colon. Endoscopic ultrasonography of the stomach and colon revealed diffuse mucosal thickening with small hypoechoic areas, corresponding to edema of the lamina propria. After treatment with parenteral hyperalimentation and tranexamic acid, his physical findings and polyposis gradually improved. This is the first report of Cronkhite-Canada syndrome in a patient with schizophrenia.

Key words: Cronkhite-Canada syndrome, endoscopic ultrasonography, schizophrenia

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Introduction

Cronkhite-Canada syndrome (CCS), first reported in 1955 by Cronkhite and Canada, is a rare gastrointestinal polyposis accompanied by diarrhea, hypoproteinemia, and ectodermal changes, such as skin hyperpigmentation, alopecia, and atrophic nail changes (1). CCS, a non-hereditary disease, is most commonly seen in middle-aged patients (2). Although more than 300 patients have been reported worldwide, the etiology of CCS remains unknown. We evaluated a case of CCS in a patient with schizophrenia that was successfully treated with parenteral hyperalimentation and tranexamic acid. We discuss the correlation between psychiatric disorders and the CCS phenotype, including the characteristic findings of endoscopic ultrasonography (EUS) seen in this patient.

Case Report

A 64-year-old Japanese man with schizophrenia exhibited waxing and waning psychiatric symptoms, for which he was followed by a local hospital for the past 35 years. Medications administered over the last two years included haloperidol (9 mg/day), biperiden (3 mg/day) and flunitrazepam (4 mg/day), and he was stable. Five months prior to admission, the patient’s laboratory data were within normal limits, with the exception of a low serum cholesterol level of 117 mg/dl (Table 1). At that time, he did not exhibit any specific symptoms, such as anemia, leukocytosis, thrombocytosis, hypoproteinemia, or hypokalemia. Three months later, he reported taste disturbances and loose bowels (5-8 times per day). After experiencing listlessness of the legs, he was transported to the emergency department by an ambulance. Head computed tomography did not reveal evidence of cerebral vessel disease; his laboratory data, however, displayed...
Figure 1. Physical findings on admission (March, 2003). Alopecia (a; frontal to central region of the head), atrophic nail changes (b), and hyperpigmentation of the skin (b, dorsum of hand).

severe hypokalemia (1.8 mEq/L), hypoproteinemia (5.0 g/dL), and hypoalbuminemia (2.5 g/dL). He was initially treated with fluid and electrolyte replacement; his leg function returned to normal within several days. As his bowel abnormalities continued, we performed endoscopic examination of the upper gastrointestinal tract and colon. We found multiple polyps with an edematous mucosa in both the stomach and colon. He was then admitted to the Medical Institute of Bioregulation Hospital, Kyushu University for a more thorough investigation and treatment.

His history of previous symptoms with the additional signs of alopecia (Fig. 1a; frontal to central region of the head), atrophic nail changes (Fig. 1b), and hyperpigmentation of the skin (Fig. 1b; dorsum of hand), the patient was diagnosed with CCS. Further laboratory examination identified anemia, mild leukocytosis, and mildly increased C-reactive protein levels (Table 1). Serum IgE levels were 1,200 IU/ml [normal range(nl): <250]; idiosyncratic IgE examination could not identify any allergens. Serum mineral levels of zinc, manganese, and copper were decreased at 49 μg/dl (nl: 65-110), 0.6 μg/dl (nl: 0.8-2.5), and 49 μg/dl (nl: 68-128), respectively. IL-4 levels had increased to 8.0 pg/ml (nl: <6.0). Analysis of the plasma concentrations of 41 serum amino acids discovered that the levels of tryptophan and cystine were significantly decreased to 20.2 nmol/ml (nl: 37-75) and 16.9 nmol/ml (nl: 29-49), respectively (Table 1). Alpha-antitrypsin clearance, a readout of intestinal absorption, gave an absorption rate of 18.9 ml/day, which is
Figure 2. Endoscopic findings of the gastrointestinal tract on admission. a; the stomach revealed mucosal edema and diffuse polyposis with irregularly-sized, hemispherical elevated lesions. b; endoscopic findings of the colon revealed multiple polyposis, with individual polyps measuring less than 25 mm.

Figure 3. Histological findings of the stomach (HE stain, ×40). Inflammatory polyps were sessile lesions composed of cystically dilated irregular glands within the lamina propria, which was expanded by edema and an inflammatory infiltrate.

Figure 4. Endoscopic ultrasonographies (EUS) findings of the stomach. Thickening of the mucosae, but not submucosal areas was observed. Arrows indicate hypoechoic areas. The colon exhibited similar changes.

Endoscopic studies of gastrointestinal tract exhibited polyposis with edematous mucosae of the stomach (Fig. 2a) and colon (Fig. 2b). A small number of polyps were also observed within the small intestine. Histopathological analysis revealed (Fig. 3) that all of the polyps were benign. These inflammatory sessile polyps were composed of focally dilated irregular foveolar glands within the lamina propria, which had expanded due to edema with eosinophilic infiltration. The lamina propria in the superficial portion was expanded to a greater extent than that in the deeper portion. EUS of the stomach and colon indicated thickening of the mucosa and small hypoechoic areas in the dilated mucosa of both the stomach (Fig. 4) and colon. Immunostaining with monoclonal antibodies specific for CD4, CD8, and CD56 revealed non-specific inflammatory changes. Cells infiltrating the gastric mucosae were primarily CD4-positive cells, with far fewer CD8- or CD56-positive cells.

As initial treatment, we administered intravenous hypera-limentation (IVH) with amino acids and minerals and oral vancomycin hydrochloride (2 g/day). We avoided giving corticosteroid therapy because of his intestinal infection with methycillin-resistant *Staphylococcus aureus* (MRSA) and the possibility of exacerbation of the patient’s schizophrenia. One month later, while his intestinal infection had resolved, the loose bowels, hypoalbuminemia, and polyposis persisted. Oral administration of anti-plasmin (tranexamic acid: 750 mg/day) was begun, which rapidly improved the patient’s loose bowels and hypoalbuminemia (Fig. 5). Four months later, his serum mineral and amino acids levels had improved, and his IgE and IL-4 levels had decreased (Table 1). His physical signs were significantly improved (Fig. 6a and b);
his endoscopic findings demonstrated improvement in the mucosal edema and a decreased number of polyps in the stomach and colon (Fig. 7). EUS findings also confirmed a reduction in mucosal thickening. The patient was then started on an oral elementary diet. Five months later, he began eating a regular diet while continuing oral administration of anti-plasmin. He has remained well for the past eight months without a recurrence of symptoms.

**Discussion**

The etiology of CCS remains unclear. Goto et al (2) reported that stresses, such as excessive physical exertion and mental strain, may trigger this syndrome. He also reported a frequency (3%) of concurrent psychiatric disorders in patients with CCS. A case of CCS associated with schizophrenia, however, has not previously been reported. Multiple case reports (3-5) have detailed patients with inflammatory bowel disease associated with schizophrenia; the relationship between psychiatric illness and the etiology of the GI disease remains unclear. Recently, acute brain syndrome as a consequence of CCS was reported (6) to be caused by the lack of electrolytes and important nutrients resulting from malabsorption. In the case reported here, however, schizo-
PhreniaprecededtheonsetofCCSbymorethan30years.
Webycouldnotfindadirectassociationbetweenthesetwodiseases,thementalstressofhislong-standingpsychiatricillnessmayhavecontributedtotheonsetofCCS.Indeed,hispsychiatricsymptomsgotslightlyworsejustpriorittothisepisodeofCCS.Wehypothesizethattheworseningofhis schizophrenia served as the trigger for the crisis of CCS.

Lavrey et al (7) and Filloux et al (8) reported phenothiazine-induced acute colitis in patients receiving butyrophenones. In the present case, the initial examination documented increased levels of serum IgE and IL-4, which decreased after treatment. Although IL-4 is a cytokine that promotes IgE secretion, we could not identify any targeted allergens by idiosyncratic IgE examination. As eradication of MRSA did not influence the GI manifestation of disease, we hypothesized that CCS was not triggered by an intestinal infection in this patient.

Makiyama et al (9) reported that gastrointestinal endoscopy of patients with CCS revealed irregular-sized, reddish, small and hemispherical elevated lesions. Histology of a polyp biopsy demonstrated cystic dilatation of the glands with hypersecretion, dilatation of the lymphatics, marked edema of the interstitium, and cellular infiltration. In this case, gastrointestinal colonoscopy revealed mucosal edema and diffuse polyposis with irregular-sized, hemispherical elevated lesions; the majority of the polyps measured less than 25 mm in length. These polyps, with cystically dilated spaces containing mucin, inflammatory cells, and debris, were lined by a non-neoplastic glandular epithelium. Similar cystic changes were observed in the nonpolypoid mucosa. The histological appearance of this specimen was consistent with previous reports of CCS (9).

To investigate the gastric wall thickening seen in CCS, Ward et al (10) performed EUS, identifying a thickening of the submucosa and multiple distinctive submucosal cystic structures. We also used EUS to examine the stomach and colon, discovering thickening of the mucosa, but not submucosal areas. We also identified hypoeochic areas within the dilated mucosa. Presumably, these are areas of cystic dilatation of glands exhibiting hypersecretion, a characteristic feature of CCS.

The standard regimen for CCS is daily oral administration of 30 mg prednisolone and/or enteric nutrition and multivitamin supplementation (11). Futagami et al (12) reported five cases of CCS treated with steroid pulse therapy. In all of these cases, malabsorption improved remarkably after treatment, with resolution of the diffuse gastrointestinal polyposis. Viranuvatti et al (13) described a patient that received three days of high-dose corticosteroids; treatment, however, had to be discontinued because of steroid-induced psychosis. We avoided corticosteroid therapy in this case because of his co-existing intestinal infection and preexisting psychiatric disorder. Tranexamic acid was given to the patient instead, as described by Koishi (14). Although the combination of corticosteroids and tranexamic acid is more effective (11), Goto et al (15) reported that anti-plasmin therapy could also be used effectively for CCS treatment. In this case, treatment with anti-plasmin alone was able to resolve the symptoms and intestinal disturbances rapidly in the absence of corticosteroids.

Although Goto (16) reported multiple cases of long-term survival after treatment with high caloric fat-containing parenteral nutrition, corticosteroids, and anti-plasmins, the prognosis of patients with CCS is generally poor. Approximately 20% of patients die of recurrences. Spontaneous regressions, however, were observed in 5–10% of CCS cases, regardless of treatment (13, 17, 18). The most serious complication of CCS is gastrointestinal malignancy; 15% of patients eventually develop colon cancer (19). Although this patient has remained healthy for eight months since being discharged, it
is imperative to follow this patient very carefully.

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References