

A severe course of Cronkhite-Canada syndrome and the review of clinical features and therapy in 49 Chinese patients

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We describe a severe case of Cronkhite-Canada syndrome and review the clinical features and therapy in 49 Chinese patients. A 67-year-old man who underwent severe chronic diarrhea had typical clinical manifestations of hyperpigmentation, hair loss, and dystrophic changes in the fingernails. Although sufficient nutrition support and other therapies reported in the literature were provided, the patient died of systemic failure one year later. Cronkhite-Canada syndrome is characterized by generalized gastrointestinal polyps associated with hyperpigmentation, hair loss, and onycholysis. Anemia, positive stool occult blood, serum electrolyte disturbances, and low serum proteins are the main clinical features of patients with Cronkhite-Canada syndrome. Most patients were diagnosed by esophagogastroduodenoscopy and/or colonoscopy, and polyps were found in the entire alimentary tract, except the notable exception of the esophagus. The polyp-like samples of mucosa, hyperplasia, and adenoma were characterized by acute/chronic inflammation. Four cases were complicated with cancer. The treatment of Cronkhite-Canada syndrome includes symptomatic and support therapy, administration of corticosteroids, antibiotics and acid inhibitors, therapeutic endoscopy, and surgery. While the mortality rate was reported as 47.3% (9/19), some patients may live a long life with controlled symptoms.

Key words: Cronkhite-Canada syndrome, rare disease, gastrointestinal polyps, case report

Ağır seyreden Cronkhite-Canada sendromu vakası ve 49 Çinli hastanın klinik özelliklerinin ve tedavisinin gözden geçirilmesi

Burada ağır seyreden Cronkhite-Canada sendromlu vaka sunumu ile beraber 49 Çin'li hastanın klinik bulguları ve tedavileri incelenmiştir. Atmış yedi yaşında erkek hasta ağır kronik diyare, hiperpigmentasyon, saç kaybı ve tırnaklarda distrofik değişiklikler ile başvurdu. Yeterli beslenme desteğine ve literatürdeki diğer tedavilerin uygulanmasına rağmen hasta 1 yıl içinde sistemik yetersizlik sonucu kaybedildi. Cronkhite-Canada sendromu, hiperpigmentasyon ve yaygın gastrointestinal polipler, saç kaybı ve onikoliz ile karakterizedir. Anemi gaitada gizli kan pozitifliği, serum elektrolit bozuklukları, düşük serum proteinleri ana klinik bulgularıdır. Birçok hasta özofagogastroduodenoskopi ve/veya kolonoskopi ile tanı alır. Özofagus dışında tüm sindirim sisteminde polipler görülür. Mukozadaki polip benzeri yapılarda hiperplazi, adenoma ve akut/kronik inflamasyon görülebilir. Dört hastada kanser geliştiği görülmüştür. Cronkhite-Canada sendromunun tedavisi semptomatik ve destekleyici özelliktedir, kortikosteroid uygulamaları, antibiyotikler, asit inhibitörleri, terapötik endoskopi ve cerrahiye kapsar. Mortalite sıklığı %47,3 (9/19) olarak verilmesine rağmen bazı hastalarda uzun sağ kalım mümkün olabilmektedir.

Anahtar kelimeler: Cronkhite-Canada sendromu, nadir hastalık, gastrointestinal polipler, vaka sunumu

INTRODUCTION

Cronkhite-Canada syndrome (CCS) is a rare disease characterized by generalized gastrointestinal polyps associated with hyperpigmentation, ha-

ir loss, and dystrophic changes in the fingernails. It was first reported and described by Cronkhite and Canada in 1955 (1). To date, only about 400

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case reports of CCS exist in the worldwide literature (2). The etiology of CCS remains largely unknown. Although fatigue and mental stress are the most commonly cited potential causes, surgery, pregnancy, radiotherapy, and alcoholism have been proposed as potential contributory factors (3). CCS is mainly diagnosed by its clinical manifestations and indicative histological findings, including generalized gastrointestinal polyps associated with ectodermal changes. Because of its rarity and lack of symptom control, the most efficacious therapy remains to be determined. In the literature, CCS treatment includes symptomatic and support therapy, administration of corticosteroids, antibiotics and acid inhibitors, therapeutic endoscopy, and surgery. Despite the proper therapy, the mortality rate of CCS remains very high. In the Chinese literature alone, a total of 48 cases have been reported, since the first report from the 1980s. Only a handful of articles have reviewed the characteristics of CCS in the Chinese population. In order to gain a detailed understanding of this rare disease in China, more cases need to be reported and analyzed. Here, we report a fulminant case of CCS with typical clinical manifestations. Furthermore, we review all reported 48 cases and the one case that was treated in our hospital with the aim of identifying some characteristics of CCS in Chinese patients.

A NOVEL CCS CASE TREATED in OUR HOSPITAL

Z.Y., a 67 year-old male, presented with a history of chronic diarrhea for about one month and was admitted in August 2010. He described watery stool and episodes of diarrhea that occurred about six to seven times per day accompanied by vague abdominal pain. At the same time, the patient noticed scalp hair loss and loss of skin pigmentation. The patient had a negative family history of gastrointestinal or congenital disease. On physical examination, there was hair loss on the scalp, axillary fossa, pubic areas and limbs (Figure 1-A). The color of the skin on his body was obviously darkened with the presence of a brownish pigment on the palms. The nails were dry and some nails had become detached. The remainder of the physical examination was otherwise unremarkable (Figure 1-C).

Initial laboratory data showed that the patient's albumin level was 32.0 g/L and potassium was 3.35 mmol/L. There was occult blood in the feces, and the antinuclear antibody was positive. Other

examinations such as routine bloodwork, serum tumor markers, erythrocyte sedimentation rate (ESR), ferritin, and immunoglobulins were all within the normal range. Thoracic and abdominal computed tomography (CT) revealed pulmonary emphysema, a lesion of interstitial substance, and cysts in the liver and kidney. Esophagogastroduodenoscopy found multiple nodular and strawberry-like proliferations throughout the entire stomach and duodenum, with an ulcer among the lesions. The mucosa of the fundus and body of the greater curvature showed a few injuries (Figure 2-A,B). Ultrasonic endoscopy showed thickening of the first, second and third layer of mucosa with a high-level echo (Figure 2 C). The muscularis propria was of sufficient integrity. Enteroscopy showed similar changes in the colon and rectum (Figure 2 D). Capsule endoscopy showed multiple nodular polyp-like lesions in the jejunum, with areas of edematous and hyperemic mucosa. The ileum was normal (Figure 2 E).

This combination of symptoms and examination findings led to the diagnosis of CCS. Because no standard therapy exists for Cronkhite-Canada Syndrome, we selected a treatment strategy that includes symptomatic and support therapy, administration of corticosteroids, antibiotics, and acid inhibitors. On September 15, 2010, therapeutic endoscopy was performed to remove comparatively large polyps. After a month and a half of treatment, the patient's scalp hair began to regrow. The nails, however, had detached completely. The patient's diarrhea was better controlled with upto four occurrences per day. The patient was discharged on September 28, 2010 with recommendations to continue with the corticosteroids, antibiotics, and acid inhibitor per os regimen. On October 7, 2010 and January 24, 2011 (Figure 1-B,D), the patient was re-hospitalized to treat anergy and worsening watery diarrhea with 7-8 daily occurrences. During this period, the patient's albumin level was recorded at 18.0 g/L and potassium at 2.90 mmol/L. Although sufficient nutritional support and other therapies reported in the literature were provided, the patient died of systemic failure in July 2011, one year after his first presentation.

REVIEW OF CLINICAL FEATURES and THERAPY in 49 CHINESE PATIENTS

A literature search of the CBM Web (year range: 1978-2011), WanFang Data (1982-2011) and PubMed (1950-2011) was performed to identify publi-



Figure 1. Ectodermal changes. (A), Hair from the scalp, eyebrows and eyelashes were lost; (B), the hair grew again after half a year's treatment. Also, the patient looked weaker than before; (C), the finger nails were splitting with onycholysis; (D), the nails completely lost, and only a soft, reddish nail bed remained after half a year.

cations with “Cronkhite Canada” or “generalized gastrointestinal polyposis” in the title or abstract. All identified case reports were collected, and information was extracted based on clinical manifestations, laboratory and endoscopy findings, treatment, and prognosis. A total of 48 separate cases were found in 45 publications. We included information from one un-published case (No. 47) treated in our hospital, bringing the total number of Chinese CCS cases to 49 for the years between 1985 and 2010. The epidemiological data was summarized using the Microsoft Excel spreadsheet software.

1) District distribution, sex and age

Of the 49 cases, 48 had information on patient's district of residence. Cases occurred across south and north China. More than one-half (29/48) were in Beijing (8/48), Guangdong (8/48), Shanxi (8/48)

and Shandong (5/48) provinces. The 49 cases were composed of 33 males and 16 females (2:1). The mean age of symptomatic disease onset was 58,28 years old, with a range from 21 to 77 years old. A majority (81.6%) of cases were over 50 years of age (Figure 3). No article specifically mentioned family history.

2) Clinical manifestations and physical examinations

Not all of the articles provided detailed descriptions of symptomology and physical findings of the patients. The most common symptoms included abdominal pain (28/49), diarrhea (41/49), abdominal distention (11/49), anorexia (25/49; 5 of 49 patients mentioned hypogeusia in particular), weight loss (29/49), weakness (12/49) and hemorrhage (10/49). Few patients experienced dizziness, tinnitus (3/49), convulsion, hypothyroidism, or si-

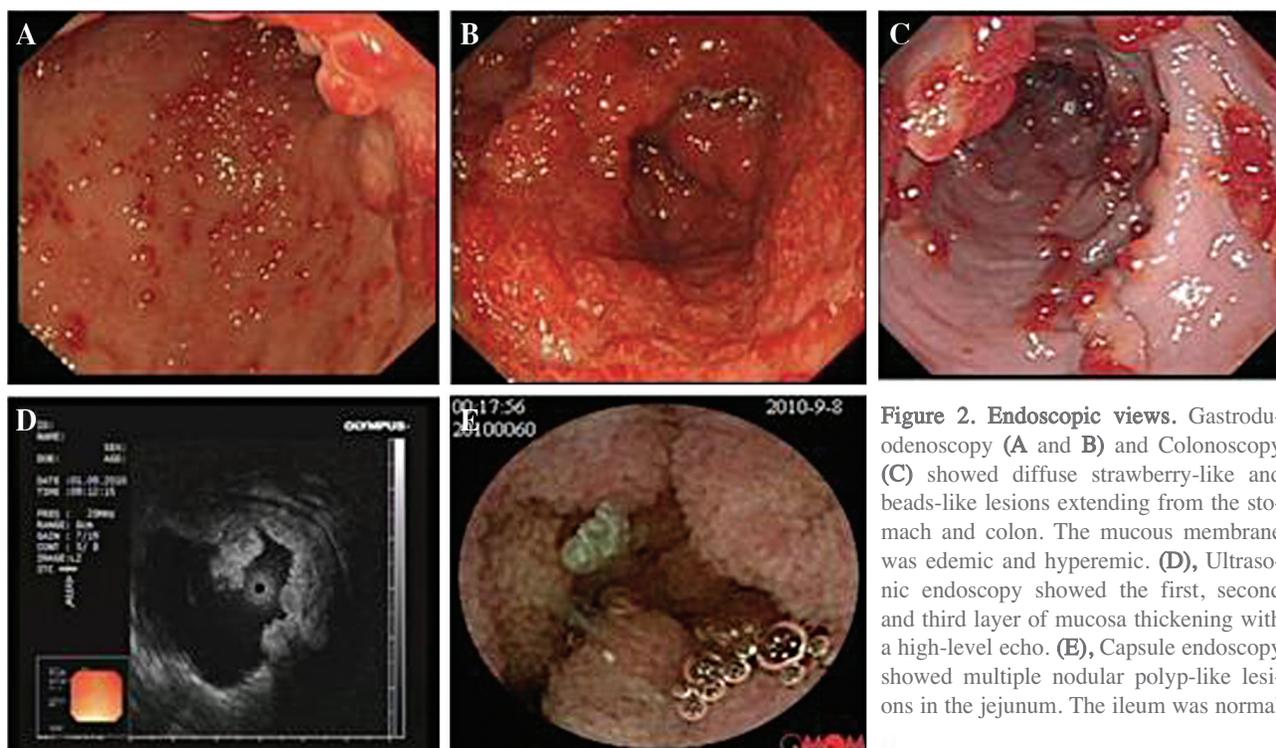


Figure 2. Endoscopic views. Gastroduodenoscopy (A and B) and Colonoscopy (C) showed diffuse strawberry-like and beads-like lesions extending from the stomach and colon. The mucous membrane was edemic and hyperemic. (D), Ultrasonic endoscopy showed the first, second and third layer of mucosa thickening with a high-level echo. (E), Capsule endoscopy showed multiple nodular polyp-like lesions in the jejunum. The ileum was normal

nus dysfunction. Diarrhea was a key manifestation of this disease. It often occurred 5-7 times per day, and sometimes more than 10 times in one day. The stools were mainly described as watery and loose, with or without blood. Abdominal pain often accompanied diarrhea. The location of pain and its intensity varied from mild local discomfort to severe diffuse pain. The order of manifestations was not specifically mentioned in most articles (Figure 4 A).

Nearly all of the reports mentioned that patients suffered hair loss (45/49), nail changes (48/49), and hyperpigmentation (42/49). Of 49 patients, 38 had all three of these symptoms. Hair loss occurred at the scalp, eyebrows, eyelashes, axillary's hairs, pubic areas, and limbs. Scalp hair was the most predominant type of hair loss reported (Figure 1-A,B). Nail changes were described as thinning, splitting, and onycholysis. Some patients had completely lost their nails, with only a soft, reddish nail bed remaining (Figure 1-C,D). Only a small number of authors described the details of hyperpigmentation, mainly as brownish changes with a clear boundary. A colored spot sometimes occurred on the face, body, limbs, palms, soles of the foot, and on the oral mucosa. Edema, which was an important finding, was not rare (19/49) and often occurred in lower limbs. Some patients also presented with anemia (6/49) (Figure 4 B).

Sex and age distribution

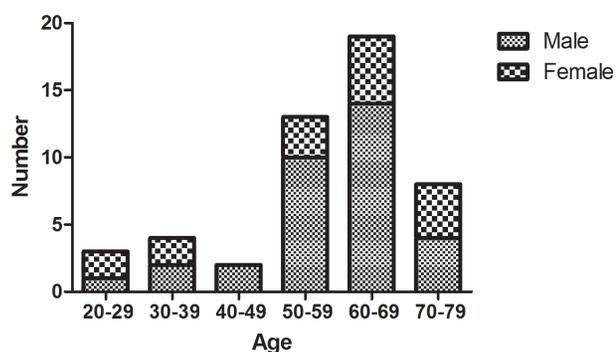


Figure 3. Sex and age (in years) distribution of Chinese patients with CCS.

3) Laboratory examinations

Each paper presented different laboratory findings as the authors only mentioned laboratory data that they considered important. As a result, the information was sporadic and we were only able to draw general conclusions for the parameters of hematology, urine and stool routine studies, electrolytes, serum proteins, liver and kidney function tests, and tumor markers.

a. Hematology

Hematological examination was mentioned in almost every CCS report. Hemoglobin data was reported for 41/49 cases; of which, 22/41 (53.7%) had

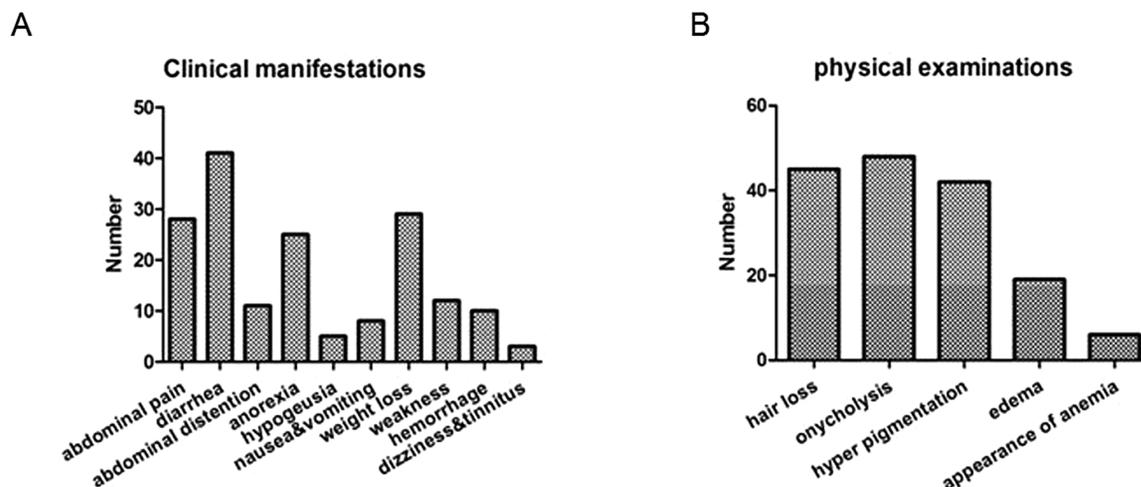


Figure 4. Clinical manifestations and physical examination of Chinese patients with CCS.

normal levels ($\text{Hb} \geq 110$ g/L). Mild anemia ($90 \leq \text{Hb} < 110$ g/L) was present in 11/41 patients with an average hemoglobin of 98g/L. Moderate anemia ($60 \leq \text{Hb} < 90$ g/L) was present in 7/41 (17.1%) cases with hemoglobin levels between 75-88 g/L (average 84 g/L). Only one case (No. 12) had severe anemia with a hemoglobin count of 59 g/L. About half of these reports mentioned white blood cell and platelet counts, which were nearly normal for all cases.

b. Routine of urine and stool

Of 49 patients, 19 had urine-related data reported, and the results from 16/19 (84.2%) were normal. Three patients had urine positive for protein. No further urine-related examination was performed in these three patients. Because of the frequency of diarrhea in CCS patients, stool examination was reported in 38 patients. Of the 38 patients with stool data, 24 (63.2%) were occult blood positive. Two of these patients (Nos. 14 and 15) had ascaris eggs in the stool. Two (Nos. 14 and 42) had bacillus difficile, salmonella and shigella in the stool.

c. Serum electrolyte

Because of malabsorption and gastrointestinal loss, many patients had serum electrolyte disturbances. In particular, serum sodium (17/49), potassium (27/49), and calcium (17/49) data were reported. Of the 17 patients with sodium data, 6 (35.3%) had hyponatremia (< 135 mmol/L), ranging from 131 to 133 mmol/L and an average of 131.9 mmol/L. Of the 27 patients with potassium data, 17 (63.0%) had low serum potassium (< 3.5

mmol/L), with data ranging from 1.45 to 3.37 mmol/L and an average of 2.87 mmol/L. Of the 17 patients with calcium data, 11 (64.7%) had low calcium levels (< 2.03 mmol/L), with data ranging from 1.4 to 1.99 mmol/L and an average of 1.77 mmol/L.

d. Serum proteins

Low serum proteins maybe a significant presentation in the biochemistry tests of patients with CCS. Total serum proteins were low (< 60 g/L) in 30 of 35 cases, and serum albumin was low (< 35 g/L) in 35 of 41 patients. Low serum total proteins levels ranged from 29 to 59 g/L, with average of 44.8 g/L. Low serum albumin levels ranged from 7 to 34.8 g/L, with an average of 22.9 g/L. In 28 patients with CCS, the serum protein levels were < 30 g/L.

e. Other examinations

Transaminase and cholesterol test results were reported for 17 patients. Blood urea nitrogen and creatinine test findings were reported for 15 patients. All of them were normal. Tumor marker test findings were reported for 16 patients; only carcinoembryonic antigen (CEA) was found to be slightly increased in patients with CCS (5-15 $\mu\text{g/L}$). Thyroid and adrenal function tests did not detect any abnormalities. Fourteen patients had immunoglobulin levels reported, and of those only one had a slightly decreased IgG index. Twelve patients had results of rheumatism index listed, including, but not limited to, antinuclear antibody (ANA) and rheumatoid factor (RF). Only one of those 12 was anti-dsDNA positive.

4) Endoscopy

Of the 49 patients with CCS in the literature, 35 underwent an esophagogastroduodenoscopy and 37 underwent a colonoscopy. In all, endoscopy results revealed diffuse sessile or pedunculated polyps with either a smooth or rough surface. The polyps varied in size, ranging from 0.2 to 15 mm in diameter. The largest polyps reached 30 to 50 mm. Some of the polyps were intertwined, like strands of beads or grapes on vines. The mucous membrane was described as edemic and hyperemic. Polyps were seen in all portions of the alimentary tract, except the esophagus. Thirty-one of the reports described the exact location of lesions. A total of 16 patients had polyps in the stomach, with no preferred location. Five cases had polyps in both, the gastric body and antrum. Another five cases had polyps exclusively in the gastric antrum. Three patients had no detectable polyps in the stomach (Nos. 39, 40 and 46). Of the 28 patients with polyps in the stomach, 26 (92.9%) also had polyps in the gastric antrum. Thirty-four of the reports described the exact location of polyps in the colon and rectum. Eleven cases only involved the colon, and 2/34 had no detectable polyps in either the colon or rectum (Nos. 22 and 30) (Figure 4).

5). Pathology

A total of 35 polyps in the stomach and 37 in the colon and rectum were sampled. All specimens were obtained by gastroscopy or colonoscopy. One sample (No. 30) was from the intestine and one (No. 6) was from the skin. The mucosal changes that were observed upon histological examination were characterized by an intact epithelium with glands being saccular and dilated, and edematous interstitial substances were present with inflammatory cell infiltrates. Of them, four cases were complicated with cancer. Three patients (Nos. 1, 13 and 18) had colon or rectal cancers, and one (No. 21) manifested as a gastric body mass. Eighteen gastric samples and 13 colon-rectum samples had obvious acute/chronic inflammation in the mucosa. Thirteen of the 35 gastric polyp-like specimens and 10 of the 37 large intestinal specimens were diagnosed as simple hyperplasia. Only 3/35 gastric samples (Nos. 12, 25 and 48) and 11/37 samples from the bowel (Nos. 3, 9, 12, 16, 18, 23, 26, 27, 33, 35 and 48) were diagnosed as adenomas (Figure 5).

6) Treatment

Because of its rarity, a ‘gold standard’ therapy has yet to be determined for CCS. In Chinese patients, a variety of pharmacologic and surgical interven-

tions have been used. Of the 49 articles examined, 37 mentioned a specific therapy used (Table 1).

a. Of the 37 articles, almost all (36/37) reported use of symptomatic and support therapy. The symptomatic therapy was mainly medical treatment for abdominal pain and diarrhea. The support therapy included intravenous fluids, enteral supplements, electrolytes, vitamins, minerals, albumin and blood transfusion. Five of 36 patients with CCS described in these articles (Nos. 5, 29, 31, 33 and 43) accepted only symptomatic and/or support therapy. Three of these five cases had an improvement in symptoms and in their general condition, while the remaining two had no change in their clinical course.

b. Corticosteroids were used in combination therapy with nutrition support and other medicines. Seventeen of these 49 patients received corticosteroids. Of those, 12 had improvement in symptoms and/or beneficial ectodermal changes and three had no change. Two of the 17 articles that reported on the use of corticosteroids did not mention the effect of this medication. Eight (Nos. 24, 27, 30, 39, 40, 41, 45 and 48) patients used corticosteroids only, except for symptomatic and support therapy. Of those eight, seven (Nos. 24, 27, 30, 39, 40, 41, 45 and 48) showed varying degrees of improvement. Only one of those eight (No. 27) had no effect from the treatment and died 39 days later. Seven of the articles specifically mentioned the improved symptoms; 3 (Nos. 30, 41, 45) patients had an improvement in only one symptom. One (No. 40) patient experienced regrowth of hair and one (No. 48) patient improved in symptoms and in ectodermal changes.

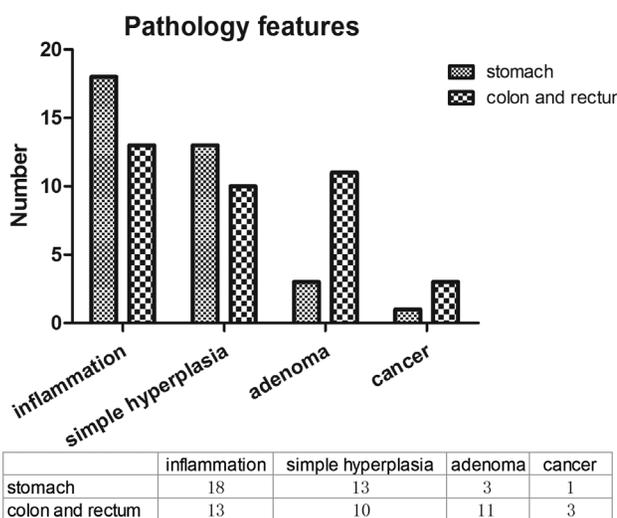


Figure 5. Pathologic features of Chinese patients with CCS.

Table 1. Treatments used with Chinese CCS patients

Treatment	Cases (Treatment with symptomatic and support therapy only)	Effect cases/ratio (Treatment with symptomatic and support therapy only)
Symptomatic and support therapy	36 (5)	27/75% (3/ 60%)
Corticosteroids	17 (8)	12/70,5% (7/87,5%)
Antibiotics	14 (4)	8/57,1% (2/50%)
Acid inhibitor	3 (1)	3/100% (1/100%)
Corticosteroids+antibiotics+ symptomatic and support therapy	6	4/66,7%
Endoscopic mucosal resection	5	4/80%

c. Additionally, four patients were treated with the NSAIDs sulfasalazine (Nos. 15, 16 and 22) and mesalamine (No. 42). Two of those four patients (Nos. 15 and 16) showed an improvement in symptoms and in the ectodermal changes.

d. About 14 patients were administered antibiotics. Eight of those had an improvement, and three had no effect mentioned in their case report. Three articles specially mentioned that these patients (Nos. 7, 15 and 16) had a bacterial infection. Four patients (Nos. 17, 28, 37 and 38) received antibiotics in addition to symptomatic and support therapy, two of whom (Nos. 37 and 38) had an improvement in their clinical manifestations.

e. Only three of the reports mentioned treating patients (Nos. 19, 47 and 49) with acid inhibitor therapy along with other medications, and all of these patients experienced an improvement in their symptoms. One (No. 19) patient was administered only cimetidine along with support therapy.

f. Endoscopic mucosal resection (EMR) was performed in five patients (Nos. 23, 25, 26, 34 and 47) to remove massively involved sections of mucosa. All of them experienced remission of symptoms and/or improved ectodermal change. However, one article (No. 25) did not mention the outcome of EMR.

g. Corticosteroid use, combined with an antibiotic and support regimen, was relatively common (Nos. 3, 9, 12, 32, 35 and 44). Four of those treated in this manner (No. 12, 32, 35 and 44), experienced improvement in symptoms.

h. Only one (No. 18) patient received surgery. Unfortunately, the reporting article did not mention the post-surgical outcome.

7) Follow-up and prognosis

A total of 19 articles recorded the data from follow-up. The follow-up period of the 19 patients in those reports ranged from three months to eight years.

Of the 19 cases, nine (47.3%; Nos. 7, 12, 13, 17, 26, 27, 34, 42 and 44) patients had died at the time of last report. The average age of these individuals was 57, with the range of 21-72 years old. The average period from onset of CCS to death was 18.7 months (range: 3-54 months). Seven of those nine patients (77.8%) had expired within 18 months. Of the nine deaths, the cause in five was mainly attributed to systemic failure (55.6%; Nos. 7, 12, 17, 26 and 27). Three died of unknown causes. One died due to a pulmonary embolism. Aside from these patients, six (Nos. 16, 22, 24, 28, 35 and 43) patients had an improvement in symptoms and lived in a stable condition until the last follow-up date, with the average follow-up being four years and ranging from seven months to eight years.

DISCUSSION

Cronkhite-Canada syndrome is a rare systemic disease with generalized polyposis and ectodermal changes, including alopecia, hyperpigmentation and onychodystrophy. Of the 400 cases that have been reported worldwide, the majority occurred in Japan. Go reviewed an epidemiological study of 154 cases reported before 1985 and found that 110 cases (71%) occurred in Japan (3). The reason that the Japanese have such a high incidence remains unknown. The mean age of patients with CCS worldwide is 59, with a range of 36 to 86 years old, and 80% of the patients are more than 50 years old (4). The demographic of CCS in China has also shown a similar distribution. The estimated incidence of CCS worldwide is one per million, according to the data from the largest study performed to date (5).

The etiology of CCS remains unknown. None of the 49 Chinese cases reviewed and described here has specifically mentioned a causative factor of the disease. Some scholars have proposed that an autoimmune factor may play a role in the onset or

progression of this disease, since some cases were associated with autoimmune diseases like lupus erythematosus, rheumatoid arthritis, and scleroderma (5). The 49 Chinese cases, however, had nearly normal results for all autoimmune clinical tests reported. Nevertheless, the role of an autoimmune factor cannot be ruled out as a contributor to the etiology of CCS. In addition, abnormalities of the endocrine system (6), and pathogenic infection [including *Helicobacter pylori* infection (7, 8)] were considered as potential etiologic agents. Evidence of familial predisposition could not be found in the existing literature. In Chinese patients with CCS, the majority (over half) came from four provinces, suggesting the existence of a regional characteristic. However, more cases are needed to analytically address this possibility.

The clinical manifestations of CCS are multiplex. Patients both, in our group and abroad, have common symptoms of diarrhea, abdominal pain, and anorexia. Hypogeusia had also been a major manifestation in some patients. In the 49 Chinese cases, hypogeusia was not rare (about 10%). Dystrophic changes in nails, alopecia and hyperpigmentation comprise the most characteristic triad observed on physical examination. Some patients had one or two of these symptoms. About 80% of Chinese patients had all three. We did not find any reports that indicate the sequence of ectodermal symptoms and clinical symptoms from the time of onset of disease. This lack of information might imply that ectodermal symptoms may be the natural manifestations of CCS.

Anemia, electrolyte disturbance, and low serum protein levels were the main findings from blood studies of the 49 Chinese cases. Most of these patients were able to recover with nutrient supplementation and therapy aimed at controlling diarrhea. This implies that the findings on bloodwork were mainly related to malabsorption and gastrointestinal loss. One report (9) used ⁹⁹Tcm gastrointestinal radionuclide imaging to demonstrate gastrointestinal loss. Four patients were reported to have slightly elevated CEA level, but none developed a gastrointestinal tumor. Some patients showed evidence of infection. Although we were unable to confirm the relationship between intestinal manifestations and infection here, it may still play a role in the etiology of CCS.

Gastrointestinal endoscopy with or without biopsy has been widely performed in patients with CCS worldwide. General polyps could be seen in the en-

terial alimentary tract, but esophageal polyps are considered rare. Daniel *et al.* (4) analyzed 55 patients from around the world and found that only one patient had esophageal polyps (2%). Likewise, we found that in Chinese patients, the gastric antrum contained the highest number of polyps. Some patients only had polyps in the gastric antrum. *Helicobacter pylori* colonization often occurs in this area. Thus, it is possible that infection maybe a causative factor.

The pathology of CCS is not specific. The polyps can be classified as inflammatory, hyperplastic, or adenomatous. This non-specificity makes the diagnosis by pathology difficult. In our case series, four cases were complicated with cancer. Unfortunately, we were unable to summarize characteristics of those tumors because of the paucity of data reported. Some scholars reviewed the worldwide literature on CCS, and found an association between CCS and gastric cancer, at a rate of 5.1% (19/374 cases). Egawa *et al.* (10) reported that a serrated adenoma was retrospectively found in 40% (10/25) of the polypoid lesions. Serrated adenomas appear as saw-toothed, elongated polyps with dilated crypts with nuclear atypia. Only 1% of polyps were serrated adenomas (11, 12). In addition, Hideaki *et al.* (13) reported that tumors in patients with CCS were different from those in common gastric cancers, based on their size and depth of infiltration. Taken together, carcinoma in CCS may not be a coincidental finding. In Chinese patients with CCS, polyps in the colon and rectum had a higher adenomatous ratio than those in stomach. This finding might imply that polyps in the large intestine were more likely to manifest clinically significant symptoms.

Since no controlled data is available, it is impossible to determine the success rate of any therapy. The treatment of this disease has yet to be analyzed for efficacy in a controlled manner. According to our analysis, symptomatic and support therapy were the fundamental therapy used, likely because of patients' symptoms and lack of nutrition. Other treatments also had an effect in improving symptoms and/or ectodermal changes. We are prone to administer a combined therapy for treating CCS in order to achieve remission of diarrhea, guard against weight loss, and correct ectodermal manifestations. Because CCS polyps may have malignant potential, some experts suggest performing a systematic resection of all polyps that are >1 cm in diameter (14).

The long-term prognosis is quite poor, according to

our review. Of 19 patient deaths reported, there was a 55.6% mortality rate in our series. Yet, some patients had a long life span with good sympto-

matic control. Some of these patients additionally experienced improved ectodermal changes and remission of polyps.

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