Hiroshima Journal of Medical Sciences
Vol. 33, No. 4, 607~614, December, 1984
HIJM 33-84

Cronkhite-Canada Syndrome

—A Case Report and Analytical Review of 37 Other Cases Reported in Japan—*)

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(Received August 24, 1984)

Key words: Cronkhite-canada syndrome, Gastrointestinal polyposis, Gastric cancer

ABSTRACT

A case of Cronkhite-Canada Syndrome (CCS), a 58-year old male, is reported. The case, who had multiple polypoid lesions in the stomach and colon, was hospitalized in a cachexic condition due to malabsorption with the chief complaint of watery diarrhea. Distal gastrectomy and total colectomy were performed due to marked watery diarrhea and the diagnosis of gastric cancer upon biopsy of the gastric polyp. After hospitalization, the case presented the typical ectodermal syndrome of hair loss, skin pigmentation and nail atrophy, but at present, ten months after his operation, his symptoms have improved and his general condition is stable and he lives a normal social life.

INTRODUCTION

Since Cronkhite and Canada reported two cases with the ectodermal syndrome of hair loss, skin pigmentation and nail atrophy and generalized gastrointestinal polyposis in 1955, reports of cases with similar symptoms have gradualy increased[3]. This syndrome, however, is comparatively rare, with only 55 cases reported in all the world as totalized by Daniel[4]. Of these, the percentage accounted for by the cases in Japan is large, the number being 32 as reported by Nonomura et al., including one case they theselves experienced[13]. The authors made a review of 38 cases, adding to this number the cases found in literature subsequently.

REPORT OF A CASE

The case is 58 year-old male, who is a judicial scrivener by profession. His past history is unremarkable. Family history shows no number with polyp of the gastrointestinal tract. With regard to his present illness, the patient had watery diarrhea 5-6 times a day and numbness of fingertips from two months previously. He had general tiredness and fever of the level of 37°C, but he had being followed up at a hospital in his neighborhood. Because the symptoms showed no signs of improvment, the patient was admitted to the hospital, where on detailed examination numerous polypoid lesions were found in the stomach, duodenum, colon and rectum, and endoscopic biopsy of the gastric polyp showed to belong to Group IV, so that adenocarcinoma was suspected. Besides, there was an aggravation of the diarrhea, with the symptom occuring even at night, and a weight loss of 9 kg in one month, the patient was referred to our clinic with consultation of the indication of surgical treatment.

Physical examination at admission revealed height of 168 cm, weight of 65.8 kg, poor nutrition, and brown pigmentations 2 cm in diameter

*) 西亀正之，高杉純好，金尾元生，奥道恒夫，田村泰三，江崎治夫：クロンクハイツ・カナダ症候群——症例報告ならびに本邦37例の集計——

Table 1. Laboratory data on the Patient

Peripheral blood		CRP	(++)
RBC (/mm³)	413×10⁴	Mantoux tbc test (mm)	7×7
Hb (g/dl)	13.3	Liver function	
Ht (%)	42	Total bil. (mg/dl)	0.5
WBC (/mm³)	8100	GOT (I. U./liter)	11
Stool examination		GPT (I. U./liter)	9
Occult blood	(++)	Al. phosphat. (I. U./liter)	66
Urine analysis	n. p.	LDH (I. U./liter)	161
Serum electrolytes		Ch. esterase (I. U./liter)	128
Na (mEq/liter)	143	Zn T T (U)	2
K (mEq/liter)	3.1	T T T (U)	0
Cl (mEq/liter)	106	Cholesterol (mg/dl)	127
Ca (mEq/liter)	3.6	Total protein (g/dl)	4.6
P (mEq/liter)	2.6	Alb. (%)	54.2
Fe (80~180 μg/dl)	228	α_1-gl. (%)	7.3
BUN (mg/dl)	6.0	α_2-gl. (%)	15.1
Creatine (mg/dl)	1.0	β-gl. (%)	11.0
Serum Amylase (Somo. U.)	69	γ-gl. (%)	12.4
Immunoglobulin		Trace minerals (postoperative 30th day)	
IgG (mg/dl)	853	Pb (less than 25.0 μg/dl)*	6.9
IgM (mg/dl)	26	Zn (80~102 μg/dl)*	64
IgA (mg/dl)	199	Cr (less than 0.65 μg/dl)*	1.38
HBs Ag	(−)	Mg (1.8~3.8 mg/dl)*	1.6
Wa-R	(−)	Cu (60~210 μg/dl)*	115
α-FP	(−)		
CEA (ng/ml)	80	( )*:norrnal value	

on the face and oral mucosa. No loss of hair or nail changes were found at admission, nor anemia or jaundice of the palpebral conjunctiva or ocular conjunctiva. No mass was palpated in the abdominal region, and liver was not palpable. Lymph nodes were not palpable in the neck or in the inguinal region. The lower extremities were devoid of edema, and tendon reflex was normal.

In laboratory tests, as shown in Table 1, serum electrolyte showed hypopotassemia and decreased calcium and inorganic P levels. Among immunoglobulins, the level of IgM was low, hypoproteinemia was evident, the level of serum total protein was 4.6 g/dl and the level of albumin 2.5 g/dl, was low. CRP was positive, and stool, which was not bloody grossly, was positive (++) on occult test. α-fetoprotein was negative, but carcinoembryonic antigen (CEA) showed an abnormally high value of 80 ng/ml. Further, gastric juice analysis showed achlorhydria and the gastrin level in blood was 140 pg/ml (normal: less than 200 pg/ml).

Fluoroscopy of the upper digestive tract showed no abnormal findings in the esophagus, but numerous fine round filling defects were found all over the stomach, with poor antral extensibility. Whiskering sign was seen in the lesser curvature of antrum (Fig. 1)[10]. A small number of polyps were seen in the first and second portions of the duodenum, but no polyps were seen in the small intestines on radiological examination. Barium enema study showed polyps 5-7 mm in diameter in entire colon (Fig. 2). Endoscopy of the stomach showed giant rugal folds extending from the esophago-gastric junction to the greater culvature and posterior wall, and large sessile type polyps, one in anterior wall of angulus, four in the antrum and one in the prepyloric area. Uniform small polyps were densely distended at other sites of stomach. No polyps were found in the third and lower portions of the duodenum. The large polyps in the angulus and the antrum were found on endoscopic biopsy to belong to Group IV, which gave us to strongly suspected adenocarcinoma.

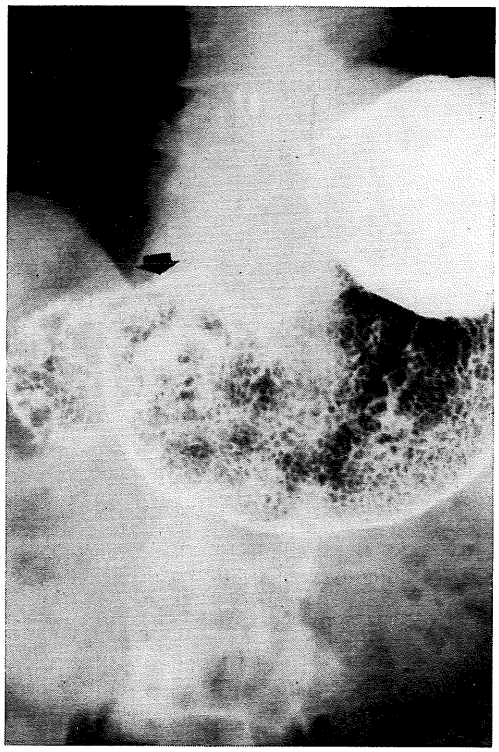

Fig. 1. Radiographic examination of the stomach. Multiple small round filling defects are seen over the entire stomach. Antral whiskering is seen, especially along the lesser curvature, (arrow).

Fig. 2. Radiographic examination of the colon. Barium enema study shows over the entire colon round filling defects 5-7 mm in size suggesting polyposis.

Colon fiberscope showed a dense growth of small polyps in entire colon, which, on biopsy, were classifiable into Group II, showing no picture of malignancy.

Because gastric cancer was strongly suspected on gastric biopsy, diarrhea and hypoproteinemia were marked, and high level of CEA was found, distal gastrectomy and total colectomy were performed and an ileac fistula was provided. The resected stomach specimen showed numerous polyps approximately 1 cm in diameter in generally and protuberance of 1-2 cm in the antrum. The protuberance, which was a cluster of polyps, was located at a site where the mucosal folds were concentrated, and the lesion was not especially hard on palpation (Fig. 3).

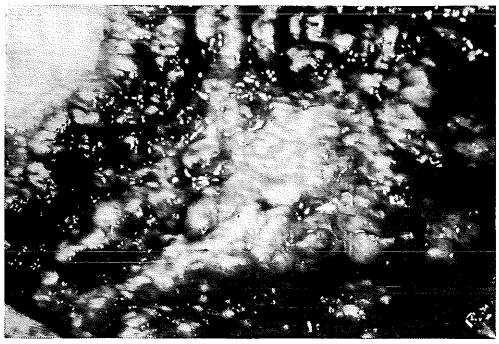

Fig. 3. Resected stomach reveals multiple polyps of various sizes. They are especially dense in the antral region, where a protuberance formed of a cluster of polyps about 1 cm in diameter is seen.

The histological findings of comparatively large polyps were same as the preoperative biopsy findings showing diffuse growth of atypical high cylindrical cells with formation of irregular glands. Depending on the site, irregularity of the gland was remarkable and the atypical cells were markedly (Fig. 4). Polyps 2-15 mm in diameter were found in entire colon, especially most numerous in the sigmoid colon, but erosion and ulceration were not present (Fig. 5).

Histologic picture of the colon polyps showed cystic dilatation of glands and exudate in the lumen. The lamina propria was edematous with infiltration of lymphocytes, plasma cells

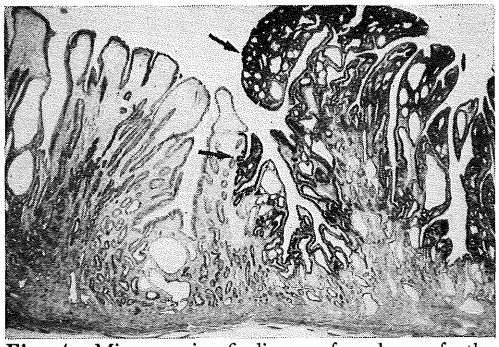

Fig. 4. Microscopic findings of polyp of the resected stomach. (H & E ×100) This is a histologic specimen of a comparatively large polyp in the antral area. There is a growth of atypical cylindrical cells with formation of irregular glands (arrow).

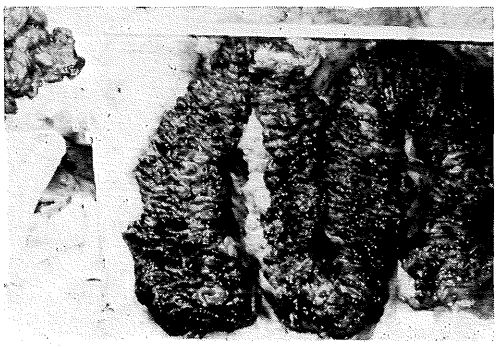

Fig. 5. Resected colon reveals scattered polyps of rather same size of 2-15 mm in diameter.

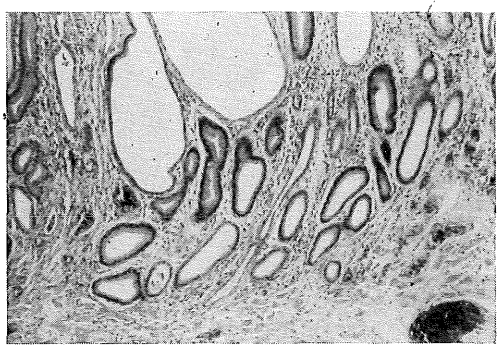

Fig. 6. Microscopic findings of polyp of resected colon. Cystic dilatation of glands is seen and exudate is present in the cyst. The interstitial area is edematous with infiltration of inflammatory cells.

and eosinophils (Fig. 6).

Because diarrhea continued postoperativelly, hyperalimentation was administered for two weeks. After two weeks, stool from the ileostomy changed to soft stool, and after one month, to solid stool. From around this time,

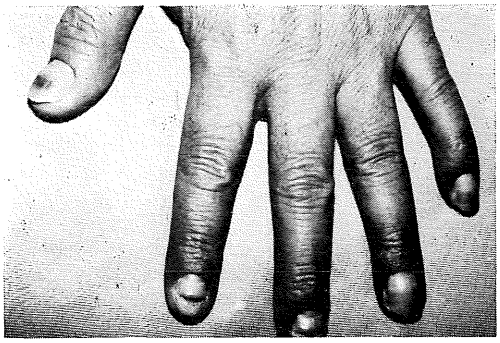

Fig. 7. Changes in fingers during hospitalization. Loss or atrophy of fingernails and dark brown pigmentation of nail beds are seen.

atrophy of fingernails and pigmentation of the nailbed occurred (Fig. 7) and hair thinned. Determination of trace minerals for possible malabsorption revealed low Zn and Mg levels as shown in Table 1. Supplementation of trace minerals and vitamines was therefore administered intravenously, but the fingernails, hair loss and skin pigmentation showed no tendency to improve. Postoperatively, there was no diarrhea, nor malabsorption, nor any change in the remnant stomach and the rectum. At present 10 months after the operation, the ectodermal syndrome is stationary and nutritional condition is good with total protein 6.6 g/dl and albumin 4.1 g/dl vitamine B_{12} in blood is 930 pg/ml (normal: 300-1000 pg/ml), there is no protein loss, and vitamin absorption is satisfactory. CEA which indicated a high value preoperatively, returned to normal with a level of less than 1 ng/ml. Further, no steroids or anticancerous drugs have been administered postoperatively; the case is being followed up with only administration of digestives.

DISCUSSION

Since two cases were first reported by Cronkhite and Canada in 1955, case reports have been made of this disease as a rare disease[3]. They describe this as a syndrome with the basic findings of (1) gastrointestinal dysfunction, malabsorption and losing syndrome of proteins and electrolytes and (2) ectodermal symptoms as pigmentation of skin, hair loss and atrophy of the fingernails and toenails, resulting from generalized gastrointestinal polyposis and replacement of the mucosa with polypoid lesion. Totalization of the cases confirming to these criteria in literature is made in the report of

Table 2. Summary of Thirty Eight Japanese Cases of Crankhite-Canada Syndrome Reported in Literature, Including the Present Case

Case	Investigator	Reported Year	Age	Sex	Diarrhea	Hair Loss	Nail Atrophy	Skin Pigmentation	Extent of Polyps*	Serum Protein/Serum Albumin (g/dl)	Outcome and Remarks	Reference**
1	Ohkita	1958	62	M	+	+	+	+	S D C R	6.3/3.6	Improved	
2	Nishiyama	1965	62	M	+	+	+	+	S D J I C R	3.4−5.9/1.79−3.54	Improved	
3	Sakida	1966	68	F	+	+	+	+	S C R	4.6−5.7/2.0−2.85	Fatal	
4	Sasagawa	1971	59	M	+	+	+	+	S C R	4.6/2.54	Fatal, Cancer in R, total colectomy	
5	Shibuya	1972	58	F	+	+	+	+	S D J I C R	3.6/2.08	Fatal, Cancer in Sigmoid and R	
6	Akagi	1972	49	M	−	+	+	+	S D I C R	3.7/2.22	Fatal	
7	Fujita	1970	62	F	+	+	+	+	S I C	5.0/2.8	Unchanged	
8	Hara	1973	65	M	−	+	+	+	S C R	4.8/2.8	Fatal	
9	Imai	1973	57	F	+	−	+	+	C D J I C R	5.8/3.08	Improved	
10	Imai	1973	57	M	+	+	+	+	S D J I C R	3.6/1.34	Unchanged	
11	Tsurumi	1974	53	F	+	+	+	+	S D J I C R	3.1/0.97	Unchanged, subtotal colectomy	
12	Kazumi	1974	62	M	+	+	+	+	S I C R	6.0−4.1/4.1−0.97	Fatal, due to postop, Ileus of appendectomy	
13	Abe	1974	56	F	−	+	+	+	S C R	6.1/3.41	Fatal, asscciated with sclerodermia	
14	Chin	1974	51	M	+	+	+	+	S C	6.5/−	Recevery	
15	Fujii	1975	57	M	+	+	+	+	S D J I C R	4.4/2.33	Fatal	
16	Yoshida	1969	35	M	+	+	+	+	S D J I C R	5.7/2.85	Fatal, γ-hemicolectomy for ileocolic invagination	
17	Ogawa	1975	43	M	+	+	+	+	S J I C R	decreased	Improved, dramatic responce to prednisone	
18	Matsunami	1975	43	M	+	−	+	+	S C	3.8/−	Exprolatory laparotomy, GI check for malignancy	
19	Uchiyama	1975	51	M	−	+	+	+	S J I C	4.6/1.84	Fatal	
20	Yokochi	1975	56	M	+	+	+	−	S J I C	decreased	Unchanged	
21	Ichikawa	1975	69	F	+	+	+	+	S D J I C	3.3/1.69	Fatal	
22	Nomura	1976	52	F	+	+	+	+	S C	5.4/−	Improved, after steroid therapy	
23	Hirabayashi	1976	75	M	+	+	+	+	S C	4.8/−	Recovery, after steroid therapy	
24	Iwasaki	1976	48	F	+	+	+	+	S	decreased	Not followed, case report	
25	Koishi	1976	65	M	+	+	+	+	S C R	decreased	Improved	
26	Fujita	1976	44	F	+	+	+	+	S D C	———	Not followed, case report	
27	Murayama	1976	60	F	+	···	···	···	S D J I C	decreased	Recovery, cancer of Sigmoid, prednine	
28	Murashima	1977	49	M	+	+	+	+	S C R	3.9/1.67	Improved	
29	Makiyama	1977	48	M	+	+	+	+	S D J I C R	5.2/2.46	Not followed, case report	
30	Mito	1977	51	M	−	+	+	+	S C R	5.9/3.76	Improved after steroid, cancer of R.	
31	Fujiwara	1978	85	F	−	+	+	+	S D J I C R	decreased	Fatal	
32	Nonomura	1980	78	M	+	+	+	+	S D J I C R	5.3/3.22	Fatal, cancer of Sig.	3
33	Takahata	1972	31	M	+	+	+	+	S D J I C R	5.4/3.0	Not followed op. for ileocolic invagination	19
34	Suzuki	1979	57	M	+	+	+	+	S D J I C R	5.0/2.7	Recovery, after steroid therapy	5
35	Miyakoshi	1980	46	F	+	+	+	+	S J C R	5.7/2.9	Recovery, spontaneously	17
36	Satoh	1981	45	M	+	+	+	+	S C R	4.7/2.7	Recovery, after anabolic hormone therapy	13
37	Kamagami	1982	67	F	+	+	+	+	? D J I C	6.0/3.72	Improved, after steroid therapy, postgastrectomy	8
38	present case	1984	58	M	+	+	+	+	S D C R	4.6/2.5	Unchanged, cancer of S., total Colectomy & Gastrectomy	

* S : Stomach, D : Duodenum, J : Jejunum, I : Ileum, C : Colon, R : Rectum

** References from case 1 to 31 were odserved in Nonomura's report[3]

Nonomura et al. who found 53 cases in the world with 31 of them Japanese[12]. Daniel et al. counted a total of 55 cases, 30 Caucasians and 25 Orientals, most of whom are reported to be Japanese[4]. It is thus a rare disease in the world, but comparatively many of them are reported from Japan. From a count of cases in Japan, Suzuki et al. reported 23 cases[17], and Nonomura reported 32 cases including their case. The authors reviewed 38 cases adding to their number the cases found in literature subsequently and the one case experienced ourselves. A summary of the cases is presented in Table 2. This disease is considered to be a non-hereditary disease which develope after middle age. In Japan, it is observed to develop over a wide range of age, from 31 to 85, but the largest number of then in the sixties with 10. Compared by sex, the frequency is higher in males with 23 as against 15 in females. Such tendencies are similar to the tendencies in other countries.

As symptoms, diarrhea was observed in 32 of the cases (84%). Other common symptoms were weight loss, abdominal pain, and general tiredness. Although the relation between the polyps and the seriousness of the diarrhea is generally influenced by the number and size of the polyps, there are reports of some cases with no diarrhea even through numerous polyps were present and of cases that suddenly improved from diarrhea even though there was no change in the polyps. However, some cases were also reported whose diarrhea was alleviated by removal of the mass of polyps, such as by total colectomy as in our case. Johnson et al. report that diarrhea is attributable to bacterial overgrowth due to deficiency of disaccharidase[6]. Many cases present moderate fevcr elevation as a result of intestinal infection, and sometimes the diarrhea and fever subside on administration of antibiotics. Some cases complain of abdominal pain, and some cases show perforation by duodenal ulcer and invagination.

Transient clowding of conciousness and sensory disturbance of extremities are also seen, which are believed to be due to the electrolyte imbalance.

As physical findings, hair loss was observed in 35 of 37 cases and nail changes in all 37 cases. Skin pigmentation was seen in 36 of 37 cases. There was no mention about ectodermal changes in one case. Thus there were only two cases that showed no skin pigmentation; the rest, or 34 of the 37 cases (92%), all had the triad of ectodermal syndromes.

The laboratory data showed moderate anemia in hematological test and, in many cases, malabsorption of vitamin B_{12} concentration in serum was often normal. Low folate level and low iron level were sometimes seen in the blood. From the results of these study, the anemia can be considered to be a secondaly disorder due to both malabsorption of the gastrointestinal tract and blood loss. A report has also been made of accentuated localized fibrinolytic activity of the gastroinsestinal tract and disappearance of the polyposis with the proteolytic enzyme inhibitor administration[19]. As regards electrolytes and minerals, many cases showed low levels of serum potassium, calcium and magnesium due to loss and malabsorption from the gastrointestinal tract. Slight decreases in zinc and copper levels were also seen. The serum protein level was decreased, though there were differences in the extent of disease, in almost all cases presenting diarrhea, and the decrease of albumin was remarked in such cases. Although there was no clear cut report concerning immunological competence, decrease of IgM was seen in many case[7]. Besides, many cases showed anacidity on gastric juice analysis. Further, some cases showed high CEA levels in the absence of definite malignant degradation[1,7].

Radiographic study demonstrated polyps in the entire gastrointestinal tract from the esophagus to the rectum, but esophageal polyps were not demonstrable histologically although two cases were reported in foreign countries[5,9]. In the cases found in Japan, the rate of polypoid lesions was 37/37 (100%) in the stomach, 19/38 (50%) in the duodenum, 22/38 (58%) in the intestine (19/38 in the jejunum, 21/38 in the ileum), 37/38 (97%) in the colon, and 26/38 (68%) in the rectum. The polyps are mostly found in the stomach and the colon, and a similar tendency is observed in other studies reported in Japan and elsewhere.

As regards the histologic characteristics of the polyp, Cronkhite-Canada first reported it is adenomatous polyp but later corrected this to inflammatory polyp[2]. Microscopically, the surface epithelium is intact, and proliferative

change of tortuous gland ahd a cystic dilatation containing proteinaceous fluid or inspissated mucus are seen. The lamina propria is edematous, with infiltration of inflammatory cells. Massive gastrointestinal bleeding is reported as the main complication in a case of CCS, but this was not found in Japan.

Invagination due to polyp in the ileocaecal region was found in two cases, for which emergency operation was performed[15].

Complication of carcinoma in the gastrointestinal tract was seen in 6/38 (16%), rectal cancer in two cases, sigmoid colon cancer in three cases, and our gastric cancer in one case. The ratio are approximately the same as reports in other countries, and cases of simultaneous multiple cancers were also seen[16]. The therapy was mostly symptomatic therapy for diarrhea, abdominal pain and fever. The method was oral or intravenous supply of electrolytes, vitamines, minerals, amino acid, albumin, and lipid. Corticosteroid was used in many cases, with which symptomatic improvement was observed and remarkable effect and improvement were reported in seven cases in Japan. Therapeutic effect of anabolic hormone has also been reported. Antibiotics have also been observed to be effective. Although nothing conclusion can be said, their effectiveness is reasonable, if, as Johnson et al. report, the symptoms are caused by infection due to intestinal bacterial overgrowth[6].

While there are cases that die of rapidly progressing cachexic condition[8,13] and cases that die of infection[1], there are also cases of implovement and reports of spontaneous recovery[11,14].

The frequently performed surgical treatment, according to reports in and outside Japan, is gastric resection, which is performed for definite diagnosis, treatment of gastroduodenal ulcer, and excision of polyps.

Colectomy is sometimes performed for alleviation of symptoms, some cases being cured by resection like our case and some cases seeming improvement with the combined use of steroids and anabolic hormone.

Complications of CCS which required surgery were two cases of invagination and six cases of cancer.

With regards to prognosis, many cases formerly died of cachexia caused by nutritional disorder, malabsorption and electrolytic disorder, but prognosis is improving recently with progress of management of the general status. In principle, the therapy is symptomatic treatment with follow up.

Although it is sometimes necessary to perform colectomy when, as in our case, mucous bloody stool and diarrhea are marked and management for low protein and electrolytic imbalance is difficult. We decided on surgical treatment for our case because the diagnosis was gastric cancer.

Gastrointestinal polyp is described as juvenile polyp in some report. While there is no malignant degeneration tendency if it is juvenile polyp, the massive proliferative mucosa in CCS is considered to be a pre-neoplastic condition and cases of complication with cancer like this reported case are seen. Therefore, we should always be careful for carcinogenesis in following up a case and perform a histologic check by biopsy of any polyp that is more than 1 cm in diameter. In review of the above results, surgical operation should be refrained from as much as possible as a symptomatic treatment and be performed when there is bowel obstruction such as invagination and development of cancer. Prophylactic colectomy against development of cancer should not be performed.

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