J Gastroenterol 2003; 38:791–795
DOI 10.1007/s00535-002-1148-6

Journal of Gastroenterology



*Case report*

# Cronkhite-Canada syndrome with colon cancer, portal thrombosis, high titer of antinuclear antibodies, and membranous glomerulonephritis

Yoji Takeuchi[1], Masahide Yoshikawa[2], Noboru Tsukamoto[1], Akira Shiroi[1], Yoshihiko Hoshida[3], Yasuhiro Enomoto[4], Toshiaki Kimura[4], Kazuo Yamamoto[4], Hideo Shiiki[5], Eiryo Kikuchi[6], and Hiroshi Fukui[6]

[1] Department of Internal Medicine, Division of Gastroenterology, Belland General Hospital, Sakai, Japan
[2] Department of Parasitology, Nara Medical University, 840 Shijo-cho, Kashihara 634-8521, Japan
[3] Department of Pathology, Osaka University Graduate School of Medicine, Osaka, Japan
[4] Department of Internal Medicine, Division of Nephrology, Belland General Hospital, Sakai, Japan
[5] First Department of Internal Medicine, Nara Medical University, Kashihara, Japan
[6] Third Department of Internal Medicine, Nara Medical University, Kashihara, Japan

A 64-year-old man, who came to us with diarrhea, presented with ectodermal changes such as hyperpigmentation, alopecia, and onychatrophy, and was affected by polyposis in the colorectum and stomach. The polyps were histologically consistent with those in Cronkhite-Canada syndrome (CCS). Interestingly, the patient also had colon cancer, as well as portal thrombosis and a high concentration of antinuclear antibody. Treatment with prednisolone ameliorated the symptoms and the gastrointestinal polyposis, while the cancer was successfully treated with a hemicolectomy. Six months after the surgery, the patient developed nephropathy, with nephrotic-range proteinuria, without recurrence of the cancer. The biopsied renal specimen showed membranous glomerulonephritis. This is a rare case of CCS associated with various complications such as colon cancer, portal vein thrombosis, a high titer of antinuclear antibodies, and membranous glomerulonephritis. Although the pathogenesis of CCS is essentially unknown, these complications might have been indicative of an underlying immunological abnormality.

**Key words:** Cronkhite-Canada syndrome, colon cancer, portal thrombosis, antinuclear antibodies, membranous glomerulonephritis

## Introduction

Cronkhite-Canada syndrome (CCS), first described by Cronkhite and Canada in 1955,[1] is a rare gastrointestinal polyposis associated with diarrhea, hypoproteinemia, and ectodermal changes, including hyperpigmentation of the skin, alopecia, and onychatrophy. The pathogenesis of CCS is essentially unknown, though emotional stress is considered to be involved.[2] Gastrointestinal (GI) polyps in patients with this syndrome are usually considered to be nonneoplastic and inflammatory in nature; however, GI carcinomas have been described in some patients.[3–13] We report a case of CCS in a patient with colon cancer that was further complicated with portal vein thrombosis (PVT), a high titer of antinuclear antibodies (ANA), and membranous glomerulonephritis (MGN).

Received: March 18, 2002 / Accepted: September 6, 2002
*Reprint requests to:* M. Yoshikawa

## Case report

A 64-year-old man was admitted to our hospital on August 16, 1999 with a 2-month history of diarrhea (four to five times/day). He suffered from watery diarrhea without abdominal pain, and had gradually noticed dysgeusia, alopecia, and loss of weight. Neither he nor his family had a history of GI disease. Physical examination revealed a well-developed male with a partial loss of capillus, hircus, and pubes, along with atrophic nails and brown pigmentation on the hands. Laboratory findings included: hemoglobin, 15.2 g/dl; hematocrit, 45.3%; serum total protein, 6.1 g/dl (albumin [alb], 62.6%; $\alpha_1$-globulin [glb], 3.5%; $\alpha_2$-glb, 7.7%; β-glb, 11.3%; Y-glb, 14.9%); total bilirubin, 0.4 mg/dl; aspartate aminotransferase (AST), 28 IU/l; alanine aminotransferase (ALT), 42 IU/l; alkaline phosphatase (ALP), 178 IU/l; γ-glutamyl transpeptidase (GTP), 25 U/l; lactate dehydrogenase (LDH), 128 IU/l; blood urea nitrogen (BUN), 11 mg/dl; serum creatinine (Cre), 0.8 mg/dl; total cholesterol, 159 mg/dl; amylase, 101 IU/l; C-reactive protein (CRP), 0.2 mg/dl, hepatitis B surface antigen

(HBsAg), (−); and hepatitis C virus-III (HCV-III), (−). Urinalysis was negative for protein, occult blood, and sugar, while feces was positive for occult blood. ANA was positive with a titer greater than 1:1280 (discrete speckled pattern). Other autoantibodies, including anti-microsomal antibody, anti-thyroglobulin antibody, rheumatoid factor (RF), and anti-smooth muscle antibody (ASMA) were not detected. The carcinoembryonic antigen (CEA) level was in the normal range, at 1.7 ng/ml. A radiologic intestinal examination revealed multiple small filling defects throughout the total colorectum; however, these were not seen in the small intestine. A colonoscopy revealed numerous polyps that were small, red, sessile, and edematous, with stromal mucosa lacking a visible vascular pattern (Fig. 1A). These were consistent with CCS polyps, by their histological features of cystically dilated tubules associated with inflammation and edema of the lamina propria. Further, a pedunculated tumor, 3 cm in diameter, was found in the ascending colon (Fig. 1B); this was diagnosed to be tubular adenoma with severe dysplasia. From the characteristic colon polyposis and several highly suggestive symptoms, such as diarrhea, hypoproteinemia, hyperpigmentation, alopecia, and onychatrophy, we made a diagnosis of CCS associated with a colon tumor, because the association between CCS and malignancy in the GI tract is known to be approximately 18% in patients with CCS.[14]

An endoscopic examination of the upper GI tract revealed a large number of reddish sessile polyps with edematous mucosa in the stomach and duodenum. Histologically, the biopsied gastric polyp specimens showed epithelial hyperplasia with cystically dilated glands and stromal edema. No polyps were found in the esophagus; however, two varices were seen in the middle and lower parts of the esophagus, both of which were linear in form and blue-colored without red-color signs. Abdominal ultrasonography (US) and computed tomography (CT) revealed a cavernous transformation of the portal vein (Fig. 2A); however, no malignancies were detected in the abdomen. Magnetic resonance angiography (MRA) disclosed a thrombus in the portal vein (Fig. 2B), whereas the inferior vena cava (IVC) and hepatic veins were not affected. Coagulation profiles on the day of admission showed no abnormal findings, including bleeding time of 2.5 min, prothrombin time of 10.7 s, partial thrombin time of 38.5 s, and fibrinogen at 283 mg/dl. In further tests performed after the discovery of the portal thrombus, anticardiolipin IgG and anticardiolipin β2 glycoprotein I were lower than the detectable limits. Antithrombin III, lupus anticoagulant, antigenic protein C, antigenic free protein S, and functional protein C values were all within normal ranges.

The diarrhea and dysgeusia symptoms were ameliorated soon after the introduction of total parenteral nutrition (TPN) and the oral administration of prednisolone (PSL), at a daily dose of 40 mg (tapered later), and his hair began to grow again. No therapy was given for the PVT and esophageal varices, because they were asymptomatic and innocent. A second colonoscopy, performed on November 24, revealed a markedly decreased number of polyps in the colon (Fig. 3A); thus, TPN was discontinued and oral intake was started. However, a type 2 tumor was found in the ascending colon where the protruding tumor had existed previously (Fig. 3B), which was histologically defined as an adenocarcinoma. On December 10, a right hemicolectomy was performed and the surgically resected specimen included an ulcerated tumor measuring 3–4 cm in size, which was defined microscopically as a colonic mucinous adenocarcinoma (Fig. 4A,B,C). The carcinoma was histologically assessed to be ss, n(−), P0H0M (−), and classified as stage II. PSL was discontinued at the end of December 1999, when the level of serum protein was total 6.2 g/dl (Alb, 4.1 g/dl) and the ANA titer was 1:320. The patient was discharged in January 2000.

The patient's clinical course after discharge was uneventful until June 2000, when proteinuria and hypercholesteremia appeared. At that time, he had nephrotic-range proteinuria, with 24-h urine protein excretion ranging from 3.5 to 4.2 g, though renal insufficiency (creatinine $>$ 1.2 mg/dl) was not found. The level of serum albumin decreased and fluctuated at around 3.0 g/dl, and the ANA titer was 1:640. He was readmitted, and a renal biopsy was performed on July 3, 2000. Deposits of IgG and C3 were observed, using immunohistochemical means, along the capillary walls of the glomeruli, and a diagnosis of membranous glomerulonephritis (MGN) was made. PSL therapy with a tapering schedule was reintroduced. Urinary protein excretion decreased gradually and was controlled at 0.3 g/24 h with PSL maintenance therapy at a daily dose of 5 mg. Recurrence of CCS-related symptoms and colon cancer metastasis have not been found during subsequent follow-up examinations.

## Discussion

Cronkhite-Canada syndrome (CCS) is a nonhereditary type of gastrointestinal polyposis associated with ectodermal changes such as hyperpigmentation, alopecia, and onychatrophy. Goto[2] reviewed 278 CCS patients that had been reported worldwide up to 1993 and found that 212 (76.3%) were Japanese. Polyps associated with CCS are considered to be nonneoplastic in nature; however, colon cancer was found in our patient. The malignancy may have been incidental, when considering the age of the patient and disease course; however,

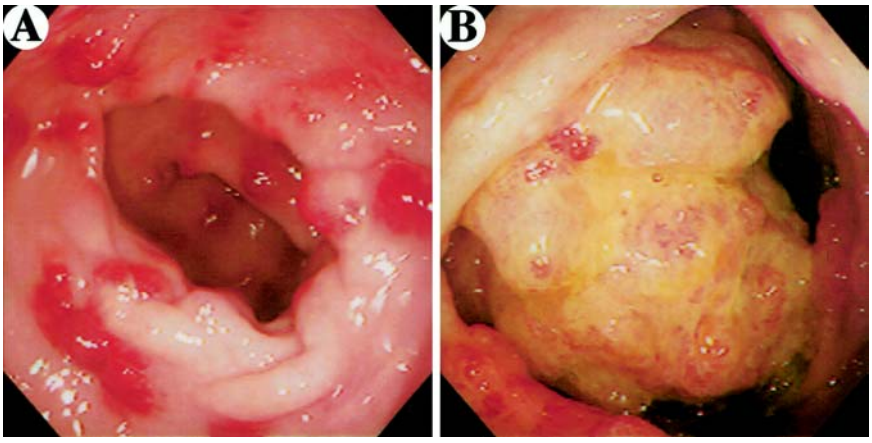


**Fig. 1A,B.** Multiple red colonic polyps (**A**) and a pedunculated tumor in the ascending colon (**B**)

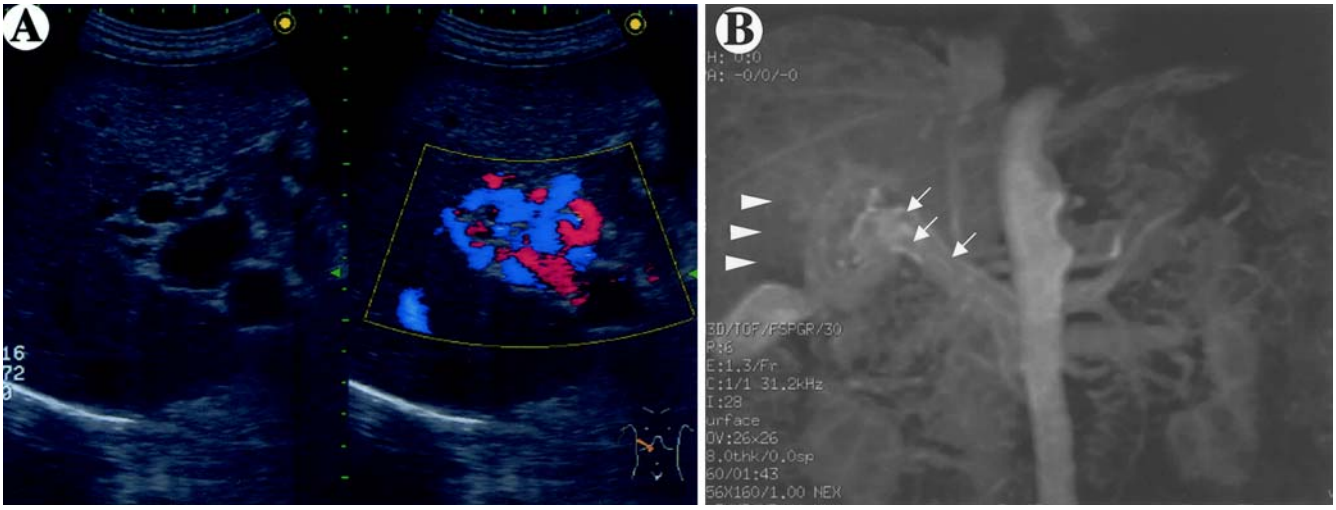


**Fig. 2.** **A** Cavernous transformation of the portal vein detected on abdominal plain (*left*) and color Doppler (*right*) sonograms. **B** Magnetic resonance angiography (MRA), showing portal vein thrombosis. The portal vein and a collateral vein are indicated by *arrows* and *arrowheads*, respectively

an accumulation of reports documenting CCS complicated with GI malignancy, including the present case, raises the idea that this association is not incidental and that GI malignancy may occur more commonly than expected. According to an investigation by Goto and Shimokawa,[14] 38 of 204 (18.6%) cases of CCS were associated with GI malignancy, while a similar frequency of GI malignancy (14.5%) has also been reported for nonJapanese patients.[15] As a result, we have concluded that careful observation for GI malignancy is required in the management of CCS.

Interestingly, the present case was associated with various complications other than colon cancer. The patient was seropositive for ANA, and developed PVT and MGN. These associated complications initially led us to consider the possible involvement of an autoimmune reaction in the pathogenesis of CCS, as an association of autoimmune diseases and vasculitis in CCS has been previously documented in a few cases.[5,16,17] Kubo et al.[17] reported a patient in whom CCS developed during the course of systemic lupus erythematosus (SLE), and Murata et al.[5] noted a CCS patient complicated with chronic pityriasis lichenoides who was seropositive for ANA. However, such patients presenting with autoimmune diseases or serological abnormalities comprise only a small minority of the reported cases of CCS. Therefore, the notion that autoimmune mechanisms are involved in the pathogenesis of CCS itself is only speculative, though the associated complications in the present patient may have been indicative of underlying immunological abnormalities.

PVT is considered to be a consequence of various conditions,[18] such as liver cirrhosis, neoplasms, myeloproliferative disorders, infections, inflammatory bowel diseases, and autoimmune diseases (e.g., antiphospholipid syndrome and SLE). Among these pre-

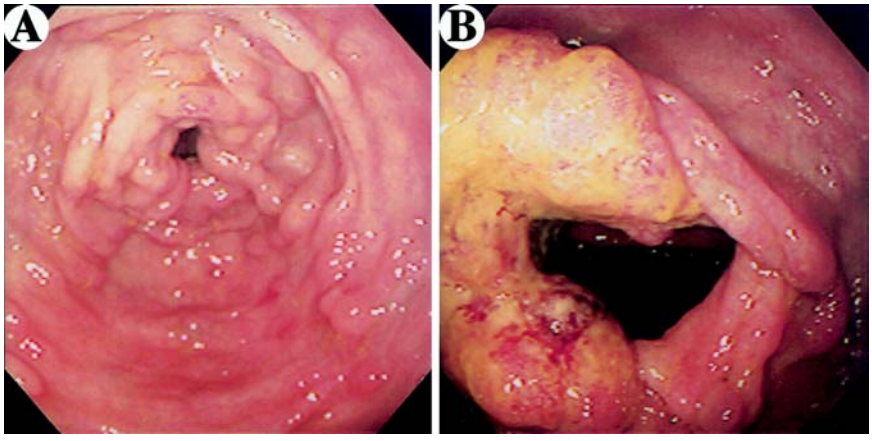


**Fig. 3A,B.** Improved colonic mucosa (**A**), and tumor in the ascending colon (**B**)

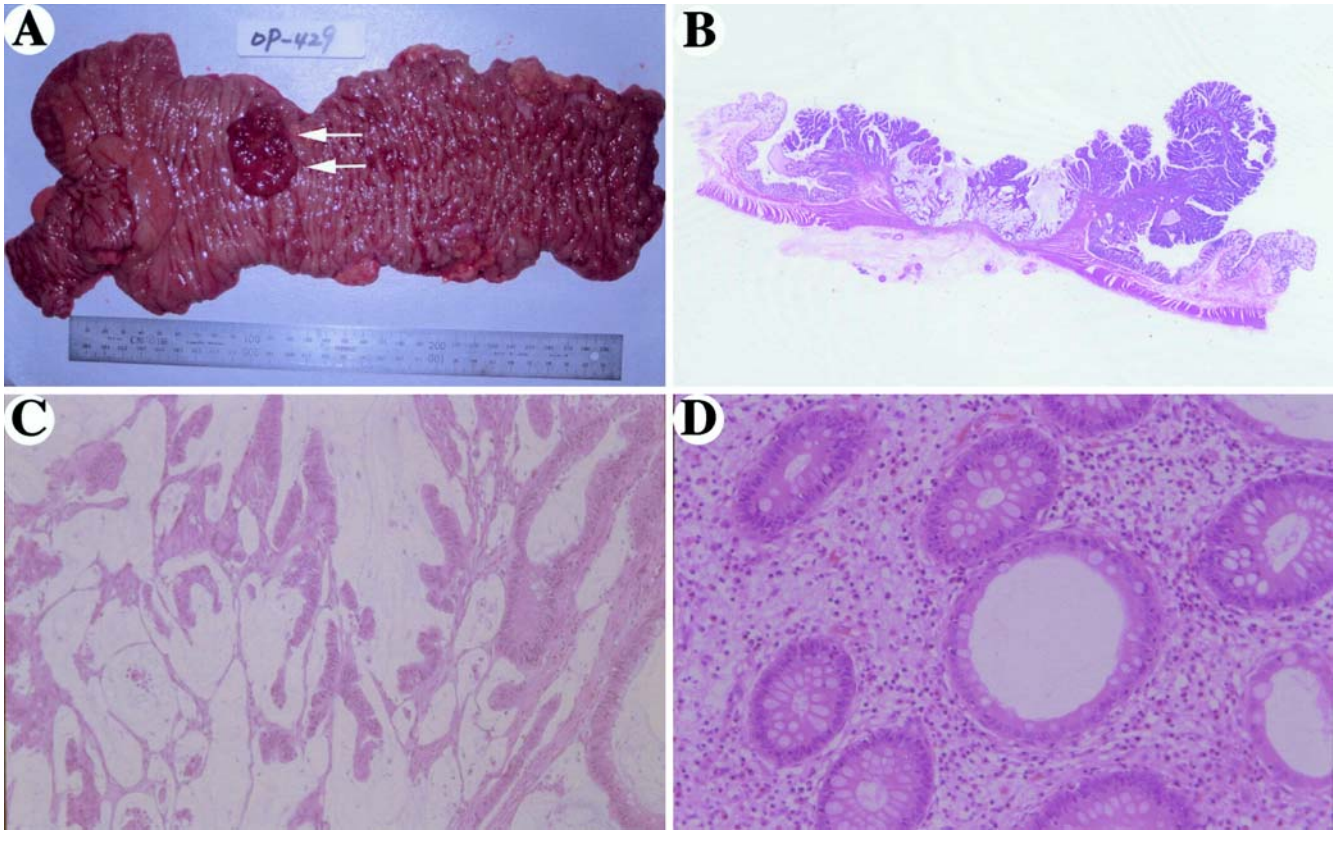


**Fig. 4.** **A** Surgically resected colon, with the tumor shown by *arrows*. **B** Histology of the tumor (shown in **A** by *arrows*) and adjacent colon tissues. **C** The tumor was histologically diagnosed as mucinous adenocarcinoma. **D** Typical histologic features of Cronkhite-Canada syndrome (CCS), presenting dilated glands surrounded by edematous lamina propria in colon tissue adjacent to the cancer. **B** H&E, ×4; **C** H&E, ×100; **D** H&E, ×100

cipitating factors, the present patient had advanced colon cancer and inflamed mucosa associated with CCS polyps in the GI tract, and he was seropositive for ANA. We think it is likely that a hypercoagulable state was induced by coagulation-activating factors derived from the cancer cells, even though no hepatic metastasis was found. However, the possibility that the inflamed mucosa in CCS might have positively affected the formation of PVT through a sequence similar to that seen in ulcerative colitis cannot be completely excluded, because PVT has been reported in patients with ulcerative colitis.[19–23] Another possibility could be the participation of an autoimmune etiology in the PVT formation; however, that did not seem to be the case in the present

patient, as antiphospholipid syndrome is completely different from the findings in his case in regard to both symptoms and laboratory data. In addition, the ANA immunostaining pattern in the present patient was discrete speckled, not homogeneous, which is known to be highly specific for SLE.

The present patient developed nephropathy with nephritic-range proteinuria, and MGN was shown in the biopsied renal specimen on an immunohistochemical examination. The majority of cases of MGN are idiopathic; however, the remainder, approximately 25% of adult patients, are associated with either neoplastic or autoimmune diseases.[24] In our patient, colon cancer had already been treated by a right hemicolectomy 6 months prior to the development of the nephropathy. According to a review focused on MGN and malignancy,[25] proteinuria in most cases is manifested prior to or at the time of malignancy diagnosis. Therefore, it is unlikely that the MGN observed in the present patient was associated with the malignancy. On the other hand, we could not completely exclude the possible participation of an autoimmune or impaired immunological reaction in the pathogenesis of MGN in this patient, as at least one CCS case is reported to have been associated with MGN, in a patient who also presented with nephrotic syndrome.[17]

Corticosteroid therapy was effective for the CCS-related symptoms, except for the GI malignancy, in the present patient. Contrary to an earlier observation, a number of recent reports have suggested a favorable prognosis with corticosteroid therapy associated with nutritional supplementation.[4,8,26,27] Although the effectiveness of corticosteroid for CCS is due to its anti-inflammatory action, we consider that such therapy is necessary to avoid a recurrence of CCS and to maintain the remission of nephropathy, especially in patients presenting with an autoimmune predisposition.

## References


1. Cronkhite LW Jr, Canada WJ. Generalized gastrointestinal polyposis. An unusual syndrome of polyposis, pigmentation, alopecia and onychotrophia. N Engl J Med 1955;252:1011–5.
2. Goto A. Cronkhite-Canada syndrome: epidemiological study of 110 cases reported in Japan. Arch Jpn Chir 1995;64:3–14.
3. Yamaguchi K, Ogata Y, Akagi Y, Sasatomi T, Ozaki K, Ohkita A, et al. Cronkhite-Canada syndrome associated with advanced rectal cancer treated by a subtotal colectomy: report of a case. Surg Today 2001;31:521–6.
4. Zugel NP, Hehl JA, Jechart G, Tannapfel A, Wienbeck M, Witte J. Colorectal carcinoma in Cronkhite-Canada syndrome. Z Gastroenterol 2001;39:365–7.
5. Murata l, Yoshikawa l, Endo M, Tai M, Toyoda C, Abe S, et al. Cronkhite-Canada syndrome: report of two cases. J Gastroenterol 2000;35:706–11.
6. Morizono S, Tanaka A, Nisiyama M, Hisano T, Ogiwara K, Nakahara S, et al. A case of Cronkhite-Canada syndrome associated with colorectal cancer (in Japanese). Nippon Shokakibyo Gakkai Zasshi (Jpn J Gastroenterol) 2000;97:1155–60.
7. Watanabe T, Kudo, M, Shirane H, Kashida H, Tomita S, Orino A, et al. Cronkhite-Canada syndrome associated with triple gastric cancers: a case report. Gastrointest Endosc 1999;50:688–91.
8. Mizukoshi E, Oba S, Sakai M, Adachi H, Inagaki Y, Morimoto H, et al. A case of Cronkhite-Canada syndrome with multiple adenomas and a carcinoma of rectum detected after improvement of polyposis due to steroid treatment—an analysis of expression of p53 protein in polyps (in Japanese). Nippon Shokakibyo Gakkai Zasshi (Jpn J Gastroenterol) 1998;95:551–6.
9. Nakatsubo N, Wakasa R, Kiyosaki K, Matsui K, Konishi F. Cronkhite-Canada syndrome associated with carcinoma of the sigmoid colon: report of a case. Surg Today 1997;27:345–8.
10. Murai N, Fukuzaki T, Nakamura T, Hayashida H, Okazaki M, Fujimoto K, et al. Cronkhite-Canada syndrome associated with colon cancer: report of a case. Surg Today 1993;23:825–9.
11. Kaneko Y, Kato, H, Tachimori Y, Watanabe H, Ushio K, Yamaguchi H, et al. Triple carcinomas in Cronkhite-Canada syndrome. Jpn J Clin Oncol 1991;21:194–202.
12. Malhotra R, Sheffield A. Cronkhite-Canada syndrome associated with colon carcinoma and adenomatous changes in C-C polyps. Am J Gastroenterol 1988;83:772–6.
13. Rappaport LB, Sperling HV, Stavrides A. Colon cancer in the Cronkhite-Canada syndrome. J Clin Gastroenterol 1986;8:199–202.
14. Goto A, Shimokawa K. Cronkhite-Canada syndrome associated with lesions predisposing to development of carcinoma. J Jpn Soc Cancer Ther 1994;29:1767–77.
15. Daniel ES, Ludwig SL, Lewin KJ, Ruprecht RM, Rajacich GM, Schwabe AD. The Cronkhite-Canada syndrome. An analysis of clinical and pathologic features and therapy in 55 patients. Medicine (Baltimore) 1982;61:293–309.
16. Parsa C. Cronkhite-Canada syndrome associated with systemic vasculitis: an autopsy study. Hum Pathol 1982;13:758–60.
17. Kubo, T, Hirose S, Aoki S, Kaji T, Kitagawa M. Canada-Cronkhite syndrome associated with systemic lupus erythematosus. Arch Intern Med 1986;146:995–6.
18. Cohen J, Edelman RR, Chopra S. Portal vein thrombosis: a review. Am J Med 1992;92:173–82.
19. Aronson AR, Steinheber FU. Portal vein thrombosis in ulcerative colitis. N Y State J Med 1971;71:2310–1.
20. Capron JP, Remond A, Lebrec D, Delamarre J, Dupas JL, Lorriaux A. Gastrointestinal bleeding due to chronic portal vein thrombosis in ulcerative colitis. Dig Dis Sci 1979;24:232–5.
21. Talbot RW, Heppell J, Dozois RR, Beart RW Jr. Vascular complications of inflammatory bowel disease. Mayo Clin Proc 1986;61:140–5.
22. Miyazaki Y, Shinomura Y, Kitamura S, Hiraoka S, Tomoda K, Nezu R, et al. Portal vein thrombosis associated with active ulcerative colitis: percutaneous transhepatic recanalization. Am J Gastroenterol 1995;90:1533–4.
23. Hagimoto T, Seo M, Okada M, Shirotani T, Tanaka K, Tomita A, et al. Portal vein thrombosis successfully treated with a colectomy in active ulcerative colitis: report of a case. Dis Colon Rectum 2001;44:587–90.
24. Wasserstein AG. Membranous glomerulonephritis. J Am Soc Nephrol 1997;8:664–74.
25. Burstein DM, Korbet SM, Schwartz MM. Membranous glomerulonephritis and malignancy. Am J Kidney Dis 1993;22:5–10.
26. Ward E, Wolfsen HC, Ng C. Medical management of Cronkhite-Canada syndrome. South Med J 2002;95:272–4.
27. Fossati M, Lombardi F, Cattaneo C, Borsa C, Colombo F. Cronkhite-Canada syndrome. A case of sustained partial-remission. Dig Liver Dis 2001;33:785–7.