Clinical Case Report

Medicine®

OPEN

Cronkhite-Canada syndrome associated with colon cancer metastatic to liver

A case report

Jing Wang, PhD, Lei Zhao, MD, Nina Ma, MD, Juanjuan Che, MD, Huihui Li, MD, Bangwei Cao, PhD*

Abstract

Rationale: Cronkhite-Canada Syndrome (CCS) is an idiopathic, nonhereditary syndrome haracterized by gastrointestinal (GI) polyposis and ectodermal changes including alopecia, onychatrophia, and pigmentation. CCS colon polyps were previously considered to be benign neoplasms. However, serrated adenoma was reported to be associated with malignant neoplasms in some cases of gastric and colorectal carcinomas, and esophageal cancers. Although malignant colon and gastric cancer have been reported in CCS, reports of distant metastasis have been rare in CCS.

Patient concerns: A 58-year-old male was referred from a nearby hospital with diarrhea and weight loss. The patient was hypoproteinemia (17.9 g/L), and multiple polyps were observed in the large intestine. He also had alopecia, onychatrophia, and dysgeusia.

Diagnoses: The presence of multiple polyps and associated symptoms of alopecia, onychatrophia, pigmentation, and dysgeusia informed the diagnosis of CCS.

Interventions: He was treated with 20mg dexamethasone acetate per day for about 3 months, 10 mg for about 9 month, 5 mg for about 1 year, and then maintained on 5 mg daily. Three years after starting treatment, colonoscopy revealed colon cancer and colon adenomas. A sigmoidectomy revealed 4 well-differentiated adenocarcinomas of the ulcerating type in the sigmoid colon, and tubularadenomas throughout the rest of the large intestine. He was treated with FOLFOX6 for 6 months. At this stage liver metastasis was found. A right hepatectomy was performed confirming hepatic metastasis of colonic adenocarcinoma, which was GPC-3(−), CD34(−), CK20(+), CDX-2(+), Hep(−), CK19(+), and CK8(+).The patient received 3 courses of hepatic arterial infusion chemotherapy.

Outcomes: The patient's status has been stable for more than 2 years, and there was no tumor recurrence or metastasis occurred.

Lessons: CCS is a rare cause of multiple polyposis most often treated with hormone therapy. Regular follow-ups are very important to ensure discovery of malignant tumors at an early stage. Studies with longer-term observations and larger sample sizes will be required to confirm these observations. However, characterization of molecular markers for the early detection of malignant transformation that might allow less invasive and more cost-effective surveillance of colon cancer is urgently sought.

Abbreviations: CCS = Cronkhite-Canada syndrome, GI = gastrointestinal.

Keywords: colon cancer, Cronkhite-Canada syndrome, liver metastasis

1. Introduction

Cronkhite-Canada syndrome (CCS), first reported by Cronkhite and Canada in 1955, is an idiopathic, nonhereditary syndrome characterized by gastrointestinal (GI) polyposis and ectodermal changes including alopecia, onychatrophia, and pigmentation.[1] CCS colon polyps were previously considered to be benign neoplasms. However, serrated adenoma was reported to be associated with malignant neoplasms in some cases of gastric[2] and colorectal carcinomas,[3,4] and esophageal cancers.[5] More than 450 cases of CCS have been described in the literature, and the incidence of associated adenomatous changes has risen from 40% to more than 70% between 2012 and 2015.[6,7] Although malignant colon and gastric cancer have been reported in CCS, reports of distant metastasis have been rare in CCS.[8]

2. Case presentation

This study was conducted in accordance with the Guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Beijing Friendship Hospital. Written informed consent was obtained from all participants.

2.1. Patient information

A Chinese male was diagnosed with CCS at 55 years of age. He was referred from a nearby hospital with diarrhea and weight loss. He reported no family history of colon cancers including familial adenomatous polyposis. The patient had smoked

Editor: Shizhang Ling.

This study was supported by the Beijing Municipal Administration of Hospitals' Youth Program (code: QML20150107) (to Jing Wang), Rising Star Program from Beijing Friendship Hospital, Capital Medical University (yyqdkt2014–10) (to Jing Wang), the Capital Health Research and Development of special (2016–4–1112) (to Jing Wang), and the traditional Chinese Medicine Science and Technology Development Fund project of Beijing (QN2015–10). The authors declare no conflicts of interest.

Department of Oncology, Beijing Friendship Hospital, Capital Medical University, Beijing, China.

** Correspondence: Bangwei Cao, Department of Oncology, Beijing Friendship Hospital, Capital Medical University, #95 Yong An Road, Xuanwu District, Beijing 100050, China (e-mail: oncology@ccmu.edu.cn).*

Medicine (2017) 96:38(e7466)

Received: 20 July 2016 / Received in final form: 15 June 2017 / Accepted: 16 June 2017

http://dx.doi.org/10.1097/MD.0000000000007466

40 cigarettes per day, and consumed 500 g liquor per day for 20 years, but quit smoking and drinking at 54 years of age. At age 55, the patient presented symptoms of chronic muddy diarrhea, 5 kg weight loss, alopecia, and nail deformities. The symptoms appeared 6 months before he went to hospital (Fig. 1, Table 1).

2.2. Laboratory examination

Blood tests revealed anemia (hemoglobin 117 g/L), hypoproteinemia (albumin 19.1 g/L), and decreased levels of IgG (640 mg/dL), IgM (48.8 mg/dL), and C3 (78.9 mg/dL). Antinuclear antibody (ANA) and extractable nuclear antigen (ENA) tests were negative, and urine tested positive for albumin. Levels of four tumor markers (CA199, CA125, CEA, and AFP) were normal.

Table 1

Patient time line.

Date	Hospital events
August 2010	Referred for diarrhea and weight loss, diagnosed with CCS
October 2011	Diagnosed with colon cancer
December 2012	Diagnosed with liver metastasis
December 2012 to June 2013	FOLFOX 12 cycles
December 2013	Partial hepatic resection
January 2014 to March 2014	Hepatic artery infusion

2.3. Endoscopy and colonoscopy

GI endoscopy revealed multiple polyps in the stomach, duodenum, and large intestine, and multiple polyps were also found by colonoscopy. Polyps were found throughout the colon,

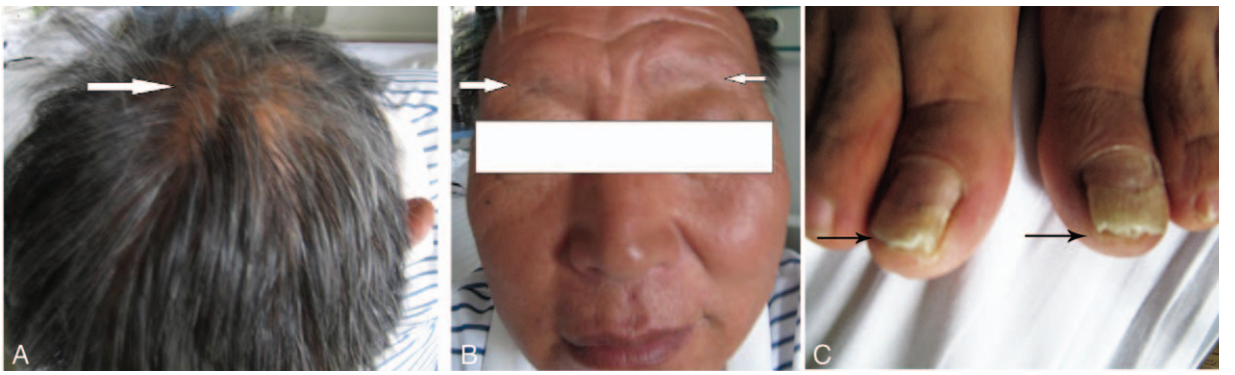

Figure 1. Physical characteristics of patient with CCS. Clinical presentation, cutaneous symptoms: (A) Alopecia (sparse head hair), (B) Milphosis (sparse eyebrows), and (C) Nail atrophy.

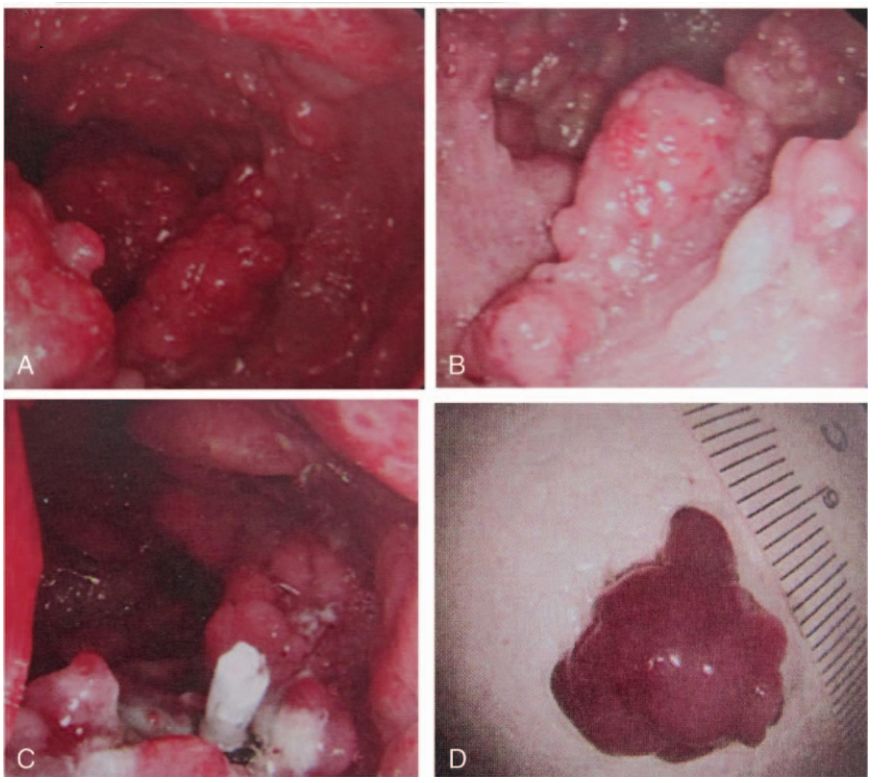

Figure 2. At colonoscopy, polyps of various sizes with surface hyperemia and edema were observed. A–C, Numerous colonic polyps. D, The largest colonic polyp was 14 mm × 4 mm.

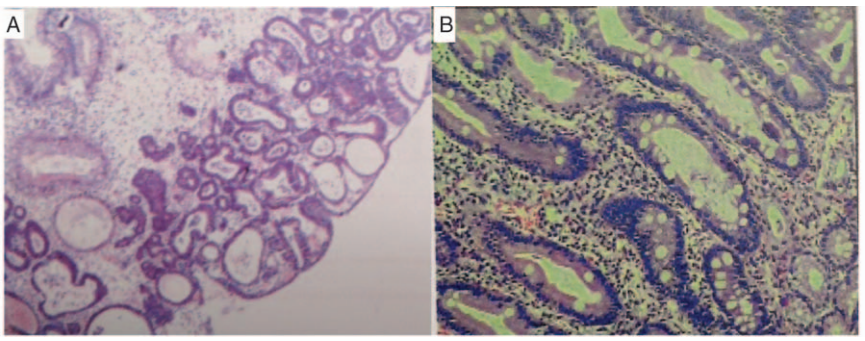

Figure 3. A, Focal low-level mucosal neoplasia. Tubular adenoma with mild hyperplasia. (HE stain ×10). B, Gastric polyps exhibiting millet fundic glands and pyloric glandular stomach mucosa, chronic inflammation with epithelial hyperplasia. (HE stain ×10).

including ileocecal region, ascending colon, transverse colon, and descending colon.

2.4. Diagnosis

The presence of multiple polyps and associated symptoms of alopecia, onychatrophia, pigmentation, and dysgeusia informed the diagnosis of CCS (Fig. 2).

2.5. Pathology

Histopathological examination revealed that the colon lesions consisted of hyperplastic polyps, and tubular adenomas. The base of the hyperplastic polyps and adjacent mucosa exhibited extensive edema, accumulation of eosinophils, and dilated glands in the lamina propria (Fig. 3A). Polyps showed glandular hyperplasia and distortion of architecture, cystic expansion with proteinaceous liquid or mucus. The mucosal lamina propria had vascular congestion, and was infiltrated by many eosinophils. These are typical histological features of CCS polyps. The histology of the gastric polyps showed millet fundic glands, and pyloric glandular stomach mucosa, chronic inflammation, with surface epithelial hyperplasia (Fig. 3B).

2.6. Treatment

The patient was administered 20 mg dexamethasone acetate for about 3 months, then 10 mg for about 9 months. When the symptoms of alopecia and nail deformities resolved, hemoglobin increased to 133 g/L, and albumin reached 42.8 g/L, the dexamethasone dose was reduced to 5 mg/day, and the patient was maintained at 5 mg/day for more than 5 years.

2.7. Malignant polyps

After diagnosis of CCS, the patient was surveilled, and underwent an annual colonoscopy. Three years after CCS diagnosis, a colonoscopy demonstrated improvement in the number and size of polyps. However, a large ulcerated irregular polyp (3 × 4 cm) was discovered 30 cm proximal to the anus in the sigmoid colon. As so many polyps were difficult to be removed, only the largest polyps were biopsied. Histopathological examination of biopsies revealed high-level intramucosal neoplasia with tubular adenoma structure, but the epithelial hyperplasia and cellular morphology did not indicate intramucosal carcinoma, and did not penetrate the mucosa (Fig. 4). Levels of CA199, CA125, and CEA were elevated (12.9 U/mL, 6.5 U/mL, and 7.56 ng/mL, respectively). The AFP level remained normal (Fig. 5). A CT scan revealed annular narrowing of the lumen with an irregular contour, and intestinal wall rigidity (Fig. 6B) suggesting malignancy.

2.8. Sigmoid resection

As colon cancer was suspected, but limited to the sigmoid colon, a sigmoid tumor resection was performed (Fig. 6A). Histological examination of the excised tissue revealed ulcerated, well-differentiated adenocarcinomas, with invasion or the muscularis and serosa without peritumor intravascular cancer emboli. The surgical margin was negative, and 21 mesenteric lymph nodes were negative for metastases. The surrounding colonic mucosa contained tubular adenomas, and exhibited mild hyperplasia. Because the colon cancer staging was pT3N0M1 (IIA), in the absence of high risk factors, the patient did not receive any postoperative therapy, but was scheduled to be followed up regularly.

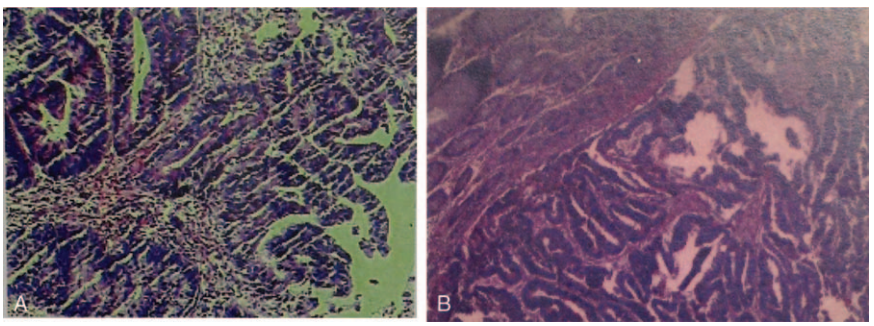

Figure 4. Ulcerated, well-differentiated colonic adenocarcinoma with invasion of the muscularis and serosa. (HE stain ×10).

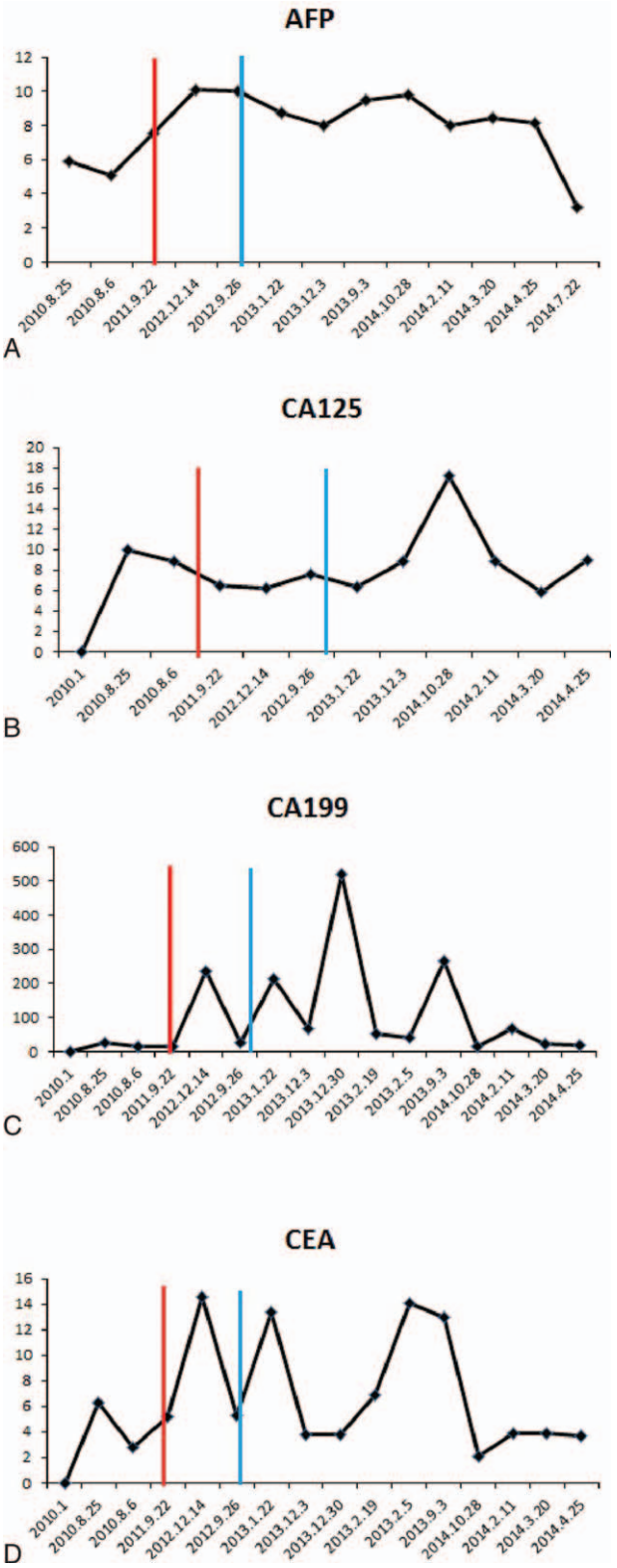

Figure 5. Tumor marker levels over time. A, AFP, (B) CA125, (C) CA199, and (D) CEA. The red line indicates the date of colon cancer diagnosis; the blue line indicates the date of liver metastasis discovery.

2.9. Liver metastasis

One year after colon cancer was diagnosed, an abdominal CT scan revealed mass lesions in the right lobe of the liver (8.8 × 4.5 cm, 36 HU on CT scan, 60 HU on CT-enhanced scan), which were considered to be metastases (Fig. 7A). The patient received 12 cycles of FOLFOX6 chemotherapy (oxaliplatin 175 mg d1 + fluorouracil 800 mg d1, fluorouracil 4000 mg civ, calcium folinate 800 mg d1) for 14 days. The liver metastasis decreased in diameter to 5.2 × 3.7 cm after chemotherapy (Fig. 7B). The patient underwent partial hepatic resection of a 5 × 3 × 4 cm grey, solid, nodular mass. Histological examination revealed a moderately differentiated adenocarcinoma that was GPC-3 (–), CD34 (–), CK20 (+), CDX-2 (+), Hep (–), CK19 (+), and CK8 (+). The patient underwent 3 courses of hepatic artery infusion of pirarubicin 60 mg + hydroxycamptothecine 26 mg + 5FU 500 mg for 1 month.

2.10. Follow up

This patient has been followed up every 3 months, receives annual colonoscopy, and was maintained on 5 mg/d dexamethasone. His condition has been stable with no evidence of tumor recurrence at the third year of follow up.

3. Discussion

The clinical features of CCS: The average age at which CCS is diagnosed is reported to be about 60 years, and CCS has been reported to occur more often in men than women (with a male to female patient ratio of 3:2).[9] The early symptoms of CCS are nonspecific, so diagnosis of CCS is often delayed for a period from 3 months to over a year.[10] Diagnosis is usually based upon medical history, symptoms, physical examination, endoscopy, and histologic examination.[11] The most common symptoms are diarrhea, weight loss, hair loss, taste abnormalities, nail deformities, skin pigmentation, glossitis, edema, and anemia. Goto et al[10] reported that clinical manifestations of CCS can be divided into 5 types based on initial symptoms: I, diarrhea; II, taste abnormalities; III, dry mouth; IV, hair loss and nail atrophy; and V, loss of appetite, malaise, nail atrophy, hair loss, and dysgeusia in the absence of diarrhea. This patient presented with diarrhea as an initial symptom, and therefore was classified as having type I CCS. Because some clinical manifestations of CCS shared with other diseases, other causes should be considered in the differential diagnosis, such as Cowden syndrome, a disorder characterized by multiple nonmalignant tumors in the GI tract[12] and elsewhere. Cowden syndrome is associated with an increased risk of developing into certain cancers in the breast and thyroid.[12] CCS polyps have a certain malignant transformation rate.[13] CCS polyps are generally classified as juvenile type polyps, and these polyps rarely become cancerous. However, data have recently emerged suggesting that the risk of colon cancer in CCS patients ranges from 9 to 15%, with a 5-year mortality rate as high as 55%.[14] Most deaths of CCS patients were attributed to gastrointestinal bleeding, sepsis, and congestive heart failure. This patient did not exhibit bleeding, sepsis, or heart failure, but did develop colon cancer, and liver metastases. This new information should be more carefully considered when treating CCS.

CCS is thought to be an autoimmune disease. Many studies have reported that autoimmune markers such as ANA, anticardiolipin, and/or aanti Saccharomyces cerevisiae antibody are elevated in CCS. However, some patients also presented with no abnormal immunological markers.[15] This report described one such patient in whom levels of ANA, ENA,

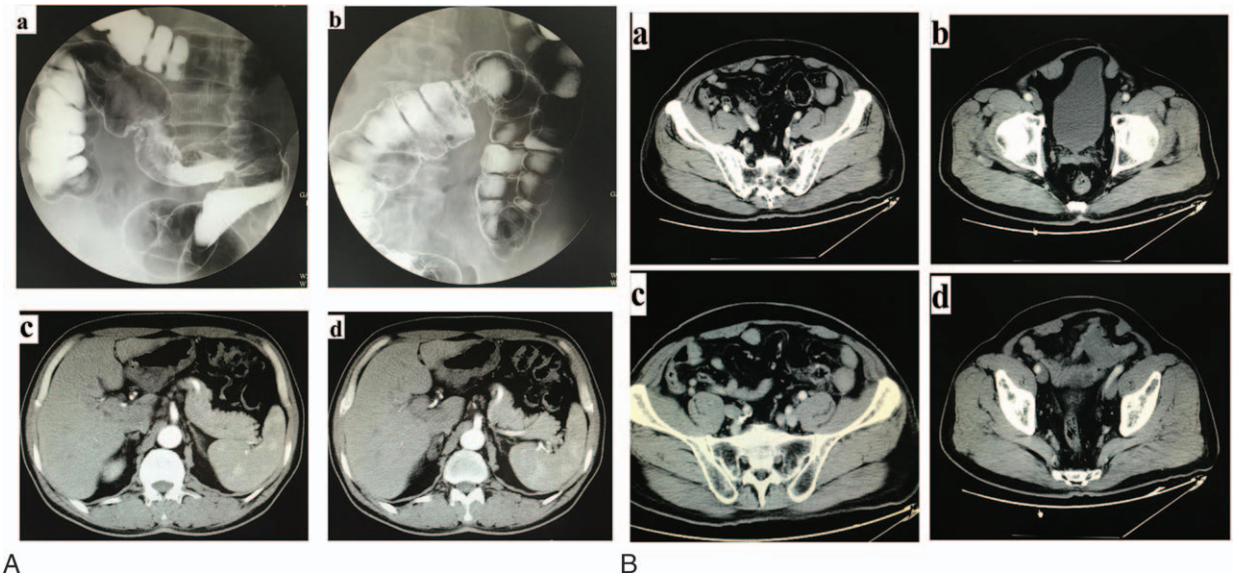

Figure 6. A, Double air-barium contrast examination revealed a narrow lumen with irregular contours, intestinal wall rigidity, and thickened mucosal folds (a–b). The abdomen CT scan revealed bowel wall thickening suggesting tumor invasion (c–d). B, The abdomen CT scan at the time of colon resection revealed an incisional hernia (a–d).

and Anti-Neutrophil Cytoplasmic Antibodies were normal on admission, and the erythrocyte sedimentation rate was normal from the time of diagnosis up to September 2015.

CCS mainly affects the stomach and colon, but can affect other areas of the digestive tract.[16] Gastric polyps and colon polyps often coexist. Polyps are usually nodular, or of irregular shape, differ in size, and are widely distributed. There is not one characteristic pathological type of CCS. However, 4 histological types of polyps are found in CCS patients: hyperplastic, tubular adenoma, juvenile, and inflammatory. It has been reported that about 12.5% polyps undergo malignant transformation,[17] highlighting the need to closely monitor these patients. The tumor markers CEA, CA125 are not particularly reliable, but can indicate occurrence, recurrence or metastasis of malignant tumors.[18]

This patient was diagnosed with colon cancer 3 years after CCS diagnosis. It is possible that within this time, a CCS polyp underwent malignant transformation. However, given the size of the malignant tumor at the time of discovery, it seems more likely that a malignant polyp was present, but undetected at CCS diagnosis.

Progressive alopecia is one of the most characteristic dermatological manifestations of CCS. Progressive alopecia involves telogen effluvium, potentially resulting from shrinkage or atrophy of hair follicles. The histopathological findings are compatible with acute nonscarring alopecia, triggered by malnutrition, in CCS. Watanabe–Okada et al[19] found that conversion from hair growth to arrest took place at quite an early stage of CCS, before hair loss was noticed.

The goals of CCS treatment include amelioration of diarrhea and weight loss, and improvement of ectodermal lesions. The most commonly used regimens include systemic hormone therapy and surgery. The effectiveness of hormone therapy has not been studied in large-scale trials, but is, nonetheless, the preferred drug regimen.[4] After gastric or bowel resection, and endoscopic polypectomies, corticosteroid treatment can provide satisfactory effects. The mechanism by which corticosteroid therapy achieves

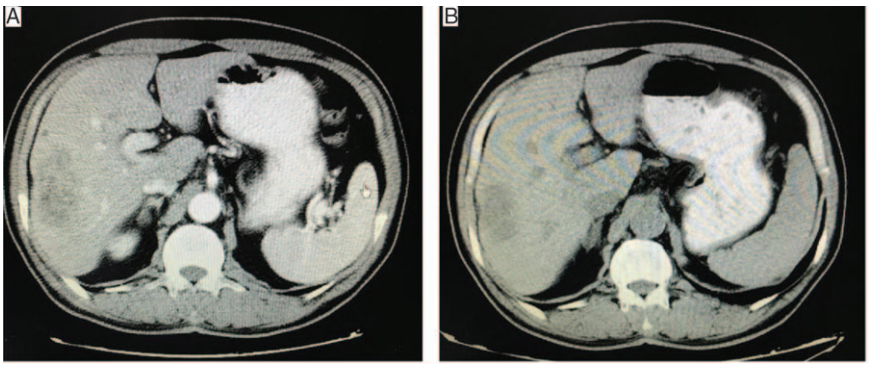

Figure 7. The abdomen CT scan revealed low density liver metastases with irregular margins. A, Focal uneven liver metastases (8.8 × 4.5 cm) before chemotherapy. B, Liver metastases (5.2 × 3.7 cm), after 12 cycles of FOLFOX6 chemotherapy: (oxaliplatin 175 mg d1+ fluorouracil 800 mg d1, fluorouracil 4000 mg (civ), and calcium folinate 800 mg d1).

its beneficial effects may involve decreasing inflammation in the GI tract, and suppressing the autoimmune response.

Corticosteroid therapy is an important component of CCS therapy, particularly for ANA positive patients. Sweetser et al[7] reported that 91% of CCS patients achieved remission, but relapse was common with steroid tapering. However, the corticosteroid doses used in the literature vary significantly, and no standard regimen has been widely adopted. Takakura et al[20] initiated CCS therapy with 30 mg prednisolone per day, and recommended the additional use of 1500 mg mesalazine per day as another anti-inflammatory agent. However, a standard dose adjustment protocol for prednisolone in CCS patients has not been established. Whether prednisolone therapy should be continued for life, or pulsed, remains controversial. In addition, some CCS patients who did not respond to steroids are reported to have been successfully treated with cyclosporine and azathioprine.[21] Treatment should, therefore, be individualized for each patient according to their symptoms and recorded response to previous therapy.

It should be noted that in the case of corticosteroid treatment, hormone reduction may be associated with the development of tumors. This patient was treated with tapering doses of dexamethasone, and the reduced dexamethasone dose may have contributed to malignant development while symptoms of CCS remained in remission. The patient was under strict surveillance, particularly for GI polyposis, but it remains possible that some lesions were overlooked during colonoscopy. Similar cases have previously been reported.[4]

4. Conclusions

CCS is a rare disease in which nonmalignant tumors develop. These tumors have the potential for malignant transformation. CCS appears to be associated with abnormalities of the ectoderm. In addition to hormone therapy, regular follow ups are crucial to ensure early discovery of malignant tumors. Molecular markers for the early detection of malignant transformation could allow less invasive and more cost-effective surveillance of colon cancer, and are urgently sought. Studies with longer-term follow-up observations and larger sample sizes will be required to confirm these observations.

References

[1] Cronkhite LWJr, Canada WJ. Generalized gastrointestinal polyposis; an unusual syndrome of polyposis, pigmentation, alopecia and onychotrophia. N Engl J Med 1955;252:1011–5.
[2] Isobe T, Kobayashi T, Hashimoto K, et al. Cronkhite-Canada syndrome complicated with multiple gastric cancers and multiple colon adenomas. Am J Case Rep 2013;14:120–8.
[3] Mason C, Quinlan C, O'Donovan M, et al. Cronkhite Canada syndrome with early colorectal carcinoma in a patient. Ir Med J 2012;105:308–9.
[4] Zhu X, Shi H, Zhou X, et al. A case of recurrent Cronkhite-Canada syndrome containing colon cancer. Int Surg 2015;100:402–7.
[5] Ito M, Matsumoto S, Takayama T, et al. Cronkhite-Canada syndrome associated with esophageal and gastric cancers: report of a case. Surg Today 2015;45:777–82.
[6] Calva D, Howe JR. Hamartomatous polyposis syndromes. Surg Clin North Am 2008;88:779–817. vii.
[7] Sweetser S, Ahlquist DA, Osborn NK, et al. Clinicopathologic features and treatment outcomes in Cronkhite-Canada syndrome: support for autoimmunity. Dig Dis Sci 2012;57:496–502.
[8] Goto A, Shimokawa K. Cronkhite-Canada syndrome associated with lesions predisposing to development of carcinoma. J Jpn Soc Cancer Ther 1994;29:1767–77.
[9] Wen XH, Wang L, Wang YX, et al. Cronkhite-Canada syndrome: report of six cases and review of literature. World J Gastroenterol 2014;20:7518–22.
[10] Goto A. Cronkhite-Canada syndrome: epidemiological study of 110 cases reported in Japan. Nihon Geka Hokan 1995;64:3–14.
[11] Daniel ES, Ludwig SL, Lewin KJ, et al. The Cronkhite-Canada syndrome. An analysis of clinical and pathologic features and therapy in 55 patients. Medicine (Baltimore) 1982;61:293–309.
[12] Rademaker J1, Kim YJ, Leibecke T, et al. Cowden disease: CT findings in three patients. Abdom Imaging 2005;30:204–7.
[13] Nonomura A, Ohta G, Ibata T, et al. Cronkhite-Canada syndrome associated with sigmoid cancer case report and review of 54 cases with the syndrome. Acta Pathol Jpn 1980;30:825–45.
[14] Yashiro M, Kobayashi H, Kubo N, et al. Cronkhite-Canada syndrome containing colon cancer and serrated adenoma lesions. Digestion 2004;69:57–62.
[15] Ota S, Kasahara A, Tada S, et al. Cronkhite-Canada syndrome showing elevated levels of antinuclear and anticentromere antibody. Clin J Gastroenterol 2015;8:29–34.
[16] Sweetser S, Boardman LA. Cronkhite-Canada syndrome: an acquired condition of gastrointestinal polyposis and dermatologic abnormalities. Gastroenterol Hepatol (N Y) 2012;8:201–3.
[17] Nakatsubo N, Wakasa R, Kiyosaki K, et al. Cronkhite-Canada syndrome associated with carcinoma of the sigmoid colon: report of a case. Surg Today 1997;27:345–8.
[18] Streppel MM, Vincent A, Mukherjee R, et al. Mucin 16 (cancer antigen 125) expression in human tissues and cell lines and correlation with clinical outcome in adenocarcinomas of the pancreas, esophagus, stomach, and colon. Hum Pathol 2012;43:1755–63.
[19] Watanabe-Okada E, Inazumi T, Matsukawa H, et al. Histopathological insights into hair loss in Cronkhite-Canada syndrome: diffuse anagen-telogen conversion precedes clinical hair loss progression. Australas J Dermatol 2014;55:145–8.
[20] Takakura M, Adachi H, Tsuchihashi N. A Case of Cronkhite–Canada Syndrome markedly improved with mesalazine therapy. Dig Endosc 2004;16:74–8.
[21] Ohmiya N, Nakamura M, Yamamura T, et al. Steroid-resistant Cronkhite-Canada syndrome successfully treated by cyclosporine and azathioprine. J Clin Gastroenterol 2014;48:463–4.