Case report

Cronkhite-Canada syndrome complicated with huge intramucosal gastric cancer

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Abstract

Cronkhite-Canada syndrome (CCS) is a rare nonhereditary disorder with gastrointestinal polyposis and associated ectodermal changes. This report documents a 59-year-old Japanese man with CCS who underwent a total gastrectomy for gastric tumors. The resected specimen showed a huge gastric adenocarcinoma with numerous polyps throughout the stomach. The cancer was pathologically limited to within the mucosa and its histological structure resembled that of hyperplasia in CCS polyps, which led us to suppose that the carcinoma had arisen from hyperplastic CCS polyps. These results urged us to study the phenotypic expression of mucins, which revealed MUC2(–) and MUC5AC(+) and supported the diagnosis of the tumor as a gastric-type well-differentiated adenocarcinoma. A literature search revealed that 32 gastric carcinomas which developed in patients with CCS were mostly limited to within the submucosa in spite of their huge sizes, and such cancer development in CCS polyposis is therefore not considered to be unusual.

Key words Cronkhite-Canada syndrome · Gastric cancer · Immunohistochemistry · Mucin

Introduction

Cronkhite-Canada syndrome (CCS) is a rare nonhereditary disorder with generalized gastrointestinal polyposis, associated with ectodermal changes such as alopecia, onychodystrophy, and hyperpigmentation [1]. Although previous reports have noted that this syndrome was rarely associated with malignancy [2], recently some reports have noted the association of CCS with carcinomas in the gastrointestinal (GI) tract [3, 4]. This report documents a Japanese man with CCS who underwent a total gastrectomy for gastric tumors,

and we studied the case in this patient regarding both the pathological findings and the phenotypic expression of mucins. Furthermore, we performed a literature search on gastric cancers associated with CCS, to elucidate the clinicopathological features of such gastric cancers associated with CCS.

Case report

A 59-year-old Japanese man had been treated for membranous glomerulonephritis (MGN) over the past 30 years. There was no family history of GI polyposis. He had been exhibiting onychodystrophy, hyperpigmentation, and hypogeusia. Gastroscopy, performed because of anemia, revealed numerous polypoid lesions of various sizes with edematous mucosa throughout the stomach (Fig. 1A). Pathologically, adenocarcinoma cells were detected in the largest polypoid lesion and an endoscopic examination of the lower GI tract showed a number of scattered small polyps in the colorectum. An upper and lower GI series revealed multiple filling defects throughout the stomach, duodenum, small intestine, and colorectum; thus, he was diagnosed with CCS complicated with gastric cancer. The results of laboratory examinations revealed anemia, hypoproteinemia (total serum protein, 3.6 g/dl; albumin, 1.8 g/dl), renal dysfunction (blood urea nitrogen, 58 mg/dl, creatinine, 4.1 mg/dl), electrolyte abnormality, and low mineral (Ca, Zn) values. The polyps in the small intestine and colon were small, and he did not have severe GI symptoms; a total gastrectomy was performed with a Roux-en-Y reconstruction. The surgical specimen revealed a giant tumor measuring 92 × 72 mm in size, with a number of polyps throughout the whole stomach (Fig. 1B). Histologically, the surface of the giant tumor consisted of well-differentiated and moderately differentiated tubular adenocarcinoma which showed a cribriform pattern (Fig. 2A). The cancerous epithelia had spread

Fig. 1. **A** Gastroscopy revealed numerous polypoid lesions of various sizes with edematous mucosa throughout the stomach. **B** The surgical specimen showed numerous polyps and a giant tumor measuring 92 × 72 mm in size (yellow arrow)

Fig. 2. **A** The surface of the Cronkhite-Canada syndrome (CCS) tumor was composed of well-differentiated and moderately differentiated tubular adenocarcinomas which showed a cribriform pattern. **B** Well-differentiated adenocarcinoma in the CCS tumor. **C** Hyperplasia with edematous stroma, cystic dilatation of the glands, and infiltration of inflammatory cells, features which are characteristic of CCS polyps. The histological structure shown in **B** resembles that shown in **C**

Fig. 3A,B. Immunohistochemical staining in gastric cancer in our patient with CCS. **A** MUC5AC is positive; **B** MUC2 is negative

superficially within the mucosal layer, covering almost the whole surface of the tumor; dysplasia was rarely found. There was no finding of lymph node metastasis or distant metastasis; therefore, the histological stage of the gastric cancer was stage IA (T1N0M0) according to the *Japanese classification of gastric carcinoma* (2nd

English edition) (website: <http://www.jgca.jp/gakkai/foreigner.html>). The histological structure of the well-differentiated adenocarcinoma (Fig. 2B) resembled that of hyperplasia, with edematous stroma, cystic dilatation of the glands, and infiltration of inflammatory cells, features that are characteristic of CCS polyps (Fig. 2C).

The identity of the pathological findings with those of CCS polyps led us to suppose that the carcinoma had arisen from hyperplastic CCS polyps.

Our notion on the pathological findings and the report by Kushima et al. [5], which referred to “adenocarcinoma arising from hyperplastic polyps,” urged us to study the phenotypic expression of the mucins in the gastric cancer tissue. This study revealed that MUC5AC was strongly positive, but MUC2 and MUC6 were negative (Fig. 3). The results supported the diagnosis of the tumor as a gastric-type well-differentiated adenocarcinoma; the concept of such tumors has recently become accepted [5]. In addition, pathology examination detected *Helicobacter pylori* infection. The patient showed marked alleviation of his hypoproteinemia (total serum protein, 6.1 g/dl; albumin, 3.3 g/dl) and was discharged subsequently without any complications.

Discussion

CCS was first reported in 1955 as generalized GI polyposis with ectodermal changes, including alopecia, hyperpigmentation, and onychodystrophy [1]. Since that time CCS has been reported mostly in Japan. Goto [6] reviewed 154 CCS cases before 1985 and reported that 110 of the patients (71.4%) were Japanese. The clinical manifestations of CCS include not only GI symptoms such as diarrhea, anorexia, weight loss, abdominal pain, and vomiting, but also ectodermal changes such as hypogeusia, onychodystrophy, hair loss, and hyperpigmentation [7]. Hypoproteinemia caused by protein loss and malabsorption have been observed frequently; furthermore, electrolyte and mineral abnormalities may be manifested. The present patient showed symptoms of onychodystrophy, hyperpigmentation, severe hypoproteinemia, electrolyte abnormality, and low mineral (Ca, Zn) values. Because he had been treated for MGN, the hypoproteinemia before the surgical resection was therefore not thought to have been caused by CCS alone. On the other hand, Sagara et al. [8] reported a CCS patient who completely recovered from hypoproteinemia after a gastrectomy; also, in the present patient, the hypoproteinemia was markedly alleviated after the total gastrectomy. This suggested that the protein had been mainly lost from the stomach in both these patients.

In our patient, the histological structure of well-differentiated adenocarcinoma in the tumor (Fig. 2B) resembled that of hyperplasia in other CCS polyps (Fig. 2C), which led us to suppose that the carcinoma had arisen from the hyperplastic CCS polyps. Kushima et al. [5] documented that 11 (78.6%) of 14 differentiated-type carcinomas in hyperplastic polyps were gastric-type adenocarcinomas. Recently, the

concept of gastric-type well-differentiated adenocarcinoma, a disease entity which is different from “intestinal-type” and which arises in nonintestinalized gastric mucosa, has been established following the discovery of *MUC* genes coding core proteins of mucin, although differentiated adenocarcinomas of the stomach have been commonly thought to arise from intestinal metaplasia [5]. These results urged us to study the phenotypic expression of mucins in the gastric cancer tissue. In our patient, MUC5AC, which is expressed in the superficial foveolar epithelia, was positive, and MUC2, which is expressed in intestinal metaplasia, was negative (Fig. 3). These results suggested that this cancer could be classified as gastric-type, not intestinal-type, well-differentiated adenocarcinoma.

CCS has rarely been reported to be associated with carcinomas [2]; however, recently, the development of cancer of the stomach in CCS patients has been reported in some articles. Egawa et al. [3] reported an association rate between CCS and gastric cancer of 5.1% (19/374 cases) and suggested that CCS was a high-risk condition for stomach malignancy. Until now, 32 CCS cases associated with gastric cancers have been reported in the literature, and all of these cases were in Japanese patients (Table 1) [3, 8, 9, 10]. One important reason that gastric carcinoma has been described solely in Japanese patients with CCS could be because of the health care surveillance system in Japan, especially regarding the progress of mass screening and regular check-ups with endoscopic examinations. Another possible reason may be the spread of *Helicobacter pylori* infection. Recently, the association of *H. pylori* infection, especially cytotoxin-associated gene A (*CagA*)-positive *H. pylori* strain infection, with the development of stomach cancer, has been actively discussed [11]; furthermore, a high incidence of gastric cancer is mostly seen in those regions where east Asian type *CagA*-positive *H. pylori* is predominant, such as in Japan [12]. It is therefore possible that *H. pylori* infection is associated with the development of gastric cancer in CCS patients. Because there have been no reports documenting *H. pylori* infection in CCS patients, except for our patient, it is difficult to discuss whether *H. pylori* infection is associated with the development of stomach cancer in CCS patients. This subject should be the next goal to be clarified.

As summarized in Table 1, in gastric cancers that developed in CCS patients, the depth of cancer invasion was limited to within the submucosa in spite of their large sizes, and they were frequently well-differentiated histological types. The invasion in our present patient was limited to within the mucosal layer in spite of its huge size as well. Considering these results, gastric cancers associated with CCS may demonstrate a low grade of malignancy. A literature search was carried out

Table 1. Reported cases of Cronkhite-Canada syndrome complicated with gastric cancer

No.	Sex	Age (years)	Macroscopic type	Greatest dimension of tumor (mm)	Depth of tumor invasion	Histological type	Reference
1	F	46	Type 1	60	T1 (M)	tub1	Nakamura et al. Stomach and Intestine 1979;14:1217–22. ^a
2	M	70	Type 1	70	T2 (SS)	tub1+sq	Yokoyama et al. Stomach and Intestine 1983;18:981–5. ^a
3	M	71	Type 1		T1 (SM)	tub1	[8]
4	M	51			T2 (SS)		Sugimura et al. Nichidai Ishi 1984;43:327. ^b
5	F	72			T1 (M)	tub2+por	Isobe et al. Prog Dig Endosc 1985;26:243–6. ^b
6	M	61			T1 (SM)		Tsushita et al. Jpn J Gastroenterol 1985;82:243–6. ^b
7	F	59	Type 1	100	T1 (M)	tub1	Uchida et al. Stomach and Intestine 1986;21:559–63. ^a
8	M	78					Koido et al. Jpn J Gastroenterology 1986;83:565. ^b
9	M	59	Type 1			tub1	Yoshida et al. J Jpn Surg Assoc 1988;49:138. ^b
10	M	68			T1 (M)	tub1	Nouchi et al. Gastroenterol Endosc 1990;32:2773. ^b
11	M	72			T1 (M)	tub1	Hasegawa et al. Gastroenterol Endosc 1990;32:2774. ^b
12	F	78					Ogawa et al. J Jpn Surg Assoc 1990;51:2790. ^b
13	M	70			T2 (SS)	por+sig	Kumano et al. Hiroshima Med J 1991;44:637–42. ^b
14	M	69	Type 0 IIc	30	T1 (SM)	tub1	[9]
15	M	54	Type 2	50	T2 (SS)	tub2	Fushida et al. J Jpn Surg Assoc 1994;55:2854–8. ^a
			Type 1	50	T1 (M)	tub1	
16	M	72	Type 2		T2 (SS)	por	Yabushita et al. Jpn J Gastroenterol Surg 1997;30:387. ^b
17	M	54					Nasu et al. J Jpn Radiol Soc 1997;57:295–6. ^b
18	M	62			T1 (M)	tub1	Daidou et al. Shiga Med J 1998;21:25–9. ^b
19	M	50	Type 3	45	T2 (MP)	tub1+tub2	Konishi et al. J Jpn Surg Assoc 1998;59:2801–7. ^a
20	M	61			T1	tub1	Tokubayashi et al. Shiga Med J 1998;20:62–3. ^b
					T1	pap	
					T1	muc	
21	M	52			T2 (MP)	tub2+por	Shiraishi et al. Gastroenterol Endosc 1999;41:1938. ^b
22	M	70	Type 1	70	T1 (SM)	tub1	[10]
			Type 1	20	T1 (M)	tub1	
			Type 1	20	T1 (M)	tub1	
23	M	73	Type 2	22	T2 (SS)	tub2	Ogami et al. J Jpn Surg Assoc 2000;61:471. ^a
24	M	52	Type 1	40	T2 (MP)	por	[3]
25	M	46	Type 1	20	T1 (SM)	tub2	Kurisu et al. Proc Jpn Soc Pathol 2000;89:364. ^b
26	M	62			T1 (SM)	muc	Kazuki et al. Proc Jpn Soc Pathol 2002;91:269. ^b
					T1 (M)	tub1+tub2	
					T1 (M)	pap	
27	M	59	Type 1		T2 (MP)	por	Kazuki et al. Proc Jpn Soc Pathol 2002;91:269. ^b
28	M	73			T2 (SS)	tub2	Ikedo et al. Jpn J Gastroenterol Surg 2003;36:1066. ^b
29	M	68	Type 1	100	T2 (SS)	por, AFP(+)	Yokoyama et al. J Jpn Surg Assoc 2003;64:3052–7. ^a
30	M	71	Type 1		T1 (M)	tub1	Hayashi et al. Rinsho Derma 2004;47:770–1. ^b
31	M	71	Type 2	30	T1 (SM)	por	Abe et al. Prog Dig Endosc 2005;67:76–7. ^b
			Type 0 IIb			tub1	
			Type 0 IIb			tub1	
			Type 1	30	T1 (M)	tub1	
32	M	59	Type 1	92	T1 (M)	tub1	Present case

According to the *Japanese classification of gastric carcinoma, 2nd English edition* (website: <http://www.jgca.jp/gakkai/foreigner.html>)

^a In Japanese with English abstract

^b In Japanese

to analyze gastric cancers in 32 Japanese CCS patients, and their clinicopathological features were compared with those of 12 533 gastric cancers treated at the Cancer Institute Hospital (Tokyo, Japan) from 1946 to 2004 [13]. This revealed that the gastric cancers in CCS patients were mostly limited to within the submucosa (T1; 24 of 36 lesions; 66.6%) in spite of their large sizes. On the other hand, 4514 lesions (36.0%) from the Cancer Institute Hospital were within T1. In a study focusing on gastric cancer cases with available informa-

tion on both their tumor depth and diameter, the average diameter of T1 gastric cancer in CCS was 47.5 mm, which was much greater than that in the common gastric cancers observed at the Cancer Institute Hospital (33.0 mm). These results may support the notion that the steps of carcinogenesis in CCS are different from those in common gastric cancers.

In clinical follow up, it is important to remember the clinicopathological features of CCS tumors, including the findings that CCS tumors are associated with malig-

nancies more frequently than was previously expected, and gastric cancers that develop from CCS tumors are mostly limited to within T1 in spite of their large sizes. Furthermore, with the findings of an immunohistochemical study of the phenotypic expression of mucins, we propose that gastric adenocarcinomas associated with CCS polyps should therefore be classified as gastric-type well-differentiated adenocarcinomas, in accordance with this recently established concept.

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