CASE REPORT

Ascending colon cancer coincident with mesenteric phlebosclerosis associated with the long-term oral intake of Chinese herb containing gardenia fruit: A case report and literature review

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Abstract Mesenteric phlebosclerosis is a recently discovered rare ischemic colon disease. The relationship between mesenteric phlebosclerosis and the use of herbal medicine containing gardenia fruit was recently reported. Although the relationship between colon cancer and mesenteric phlebosclerosis has not been described, some cases of colorectal cancer coincident with mesenteric phlebosclerosis have been reported. We treated a 63-year-old female who was diagnosed with ascending colon cancer coincident with mesenteric phlebosclerosis. She had been taking a Chinese herb containing gardenia fruit for over 18 years. The ascending colon cancer was clinically diagnosed as T2, N0, and M0 according to Japanese classification of colorectal carcinoma and the mesenteric phlebosclerosis had spread from the cecum to the descending colon. She underwent laparoscopic subtotal colectomy with en bloc removal of the regional lymph nodes, and both the ascending colon cancer and mesenteric phlebosclerosis were completely resected. The microscopic findings show that the tumor was well-differentiated tubular adenocarcinoma invading the

muscular propria with no regional lymph node metastasis, and the mesenteric phlebosclerosis lesion was characterized by marked fibrous thickening of the venous walls with calcification, marked transmural fibrosis and deposition of the collagen in the mucosa, accompanied by macrophages within the vessel walls. In literature review, 10 cases with colorectal cancer coincident with mesenteric phlebosclerosis were reported. 9 of 10 cases (90%) had cancer in the right-side colon affected by mesenteric phlebosclerosis, and 5 of 10 cases (50%) were associated with the use of a Chinese herb containing gardenia fruit. It was recently demonstrated that genipin, which is a metabolite bio-transformed from gardenia fruit, possesses carcinogenesis. We speculate that genipin may be associated with not only the development of mesenteric phlebosclerosis but also carcinogenesis in the right-side colon. In conclusion, our findings suggest that the safety of gardenia fruit should be re-evaluated, and gastroenterologists should be aware that gardenia fruit may be risk factor for not only the development of mesenteric

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phlebosclerosis but also carcinogenesis in the proximal colon.

Keywords Colon cancer · Mesenteric phlebosclerosis · Chinese herb · Gardenia fruit (*sanshishi*) · Genipin

Introduction

Mesenteric phlebosclerosis (MP) is a recently discovered rare ischemic colon disease [1]. Cases of MP have been mainly reported in Asian countries, especially Japan. MP is caused by disturbed venous return due to sclerosis in the tributaries of the superior mesenteric vein and induces the development of chronically dysfunctional colon, with symptoms such as abdominal pain, diarrhea, constipation, or ileus [2–5]. The etiology of MP has remained unclear, but recently, the relationship between MP and the use of herbal medicine containing gardenia fruit (GF) (*sanshishi*) was reported based on the results of a large-scale nationwide survey in Japan [6]. Although Chinese herb containing GF may contribute to the development of MP, the relationship between colon cancer and MP associated with GF has not been described. Thus far, a few cases of colorectal cancer coincident with MP have been reported and these sporadic reports concluded that MP has little association with colorectal cancer [7–15]. However, it was recently demonstrated that genipin, which is a metabolite bio-transformed from GF by human intestinal bacteria, possesses genotoxicity and induces the production of reactive oxygen species (ROS) and cyclooxygenase (COX)-2 expression in macrophages [16, 17]. Therefore, it cannot be denied that the use of a Chinese herb containing GF may increase the risk of developing not only MP but also a colorectal cancer.

We herein report a patient with ascending colon cancer (ACC) coincident with MP who had used Chinese herb containing GF for over 18 years.

Case presentation

A 63-year-old female was diagnosed with ACC coincident with MP. She had no symptoms that suggested colonic dysfunction, and the diagnosis was made based on positive fecal occult blood test. She had been taking kamishyoyosan (Chinese herb containing GF) for more than 18 years in order to treat symptoms of postmenopausal syndrome after she underwent total hysterectomy for myoma of uterus. There was nothing associated with cancer in her family history.

Colonoscopy showed a flat polypoid lesion approximately 40 mm in diameter in the ascending colon (Fig. 1a), and biopsy specimens pathologically revealed adenocarcinoma. The ACC was clinically diagnosed as T2, N0, and M0 according to Japanese classification of colorectal carcinoma [18] and deemed to require colectomy, such as ileocecal resection, with en bloc removal of the regional lymph nodes [19]. Colonoscopy further revealed pathognomonic dark-purple edematous mucosa with multiple erosions and ulcers from the cecum to the descending colon (Fig. 1b). A contrast enema showed the thumbprint-like appearance of the ascending colon (Fig. 2a). Abdominal computed tomography (CT) showed linear calcification of the intramural and mesenteric veins and the well-thickened colonic wall of the total right hemicolon (Fig. 2b). These image findings easily led us to diagnose the colonic lesion from the cecum to the descending colon as MP. The patient underwent laparoscopic subtotal colectomy with en bloc removal of the regional lymph nodes, ileocolostomy using functional end-to-end anastomosis, and temporary ileostomy. The intraoperative findings showed the dark-purple colonic wall from the cecum to the descending colon (Fig. 3a, b). The macroscopic findings of the resected spectrum showed a dark-purple thickened colon from the cecum to the descending colon and a type 0-IIa lesion 70 mm in diameter at the ascending colon (Fig. 3c). The microscopic findings showed

Fig. 1 The colonoscopy findings. **a** The tumor (arrow) showed a flat polypoid lesion at the ascending colon. **b** The MP showed pathognomonic dark-purple edematous mucosa with erosions and ulcers from the cecum to the descending colon

Fig. 2 The imaging findings of the MP. **a** A contrast enema showed the thumbprint-like appearance (*arrow*) of the ascending colon. **b** CT showed linear calcification of the intramural and mesenteric veins and the well-thickened colonic wall of the total right hemi-colon

Fig. 3 The intraoperative and macroscopic findings of the resected specimen. **a** The laparoscopic findings showed the *dark-purple* colonic wall from the cecum to the descending colon. **b** The gross findings showed the same images as laparoscopic findings. **c** The resected specimen showed a *dark-purple* thickened colon from the cecum to the descending colon and a type 0-IIa lesion at the ascending colon

that the primary tumor was well-differentiated tubular adenocarcinoma (tub1), invading the muscular propria (pT2[MP]), with no regional lymph node metastasis (pN0) (Fig. 4a), and the MP lesion was characterized by marked fibrous thickening of the venous walls with calcification, marked transmural fibrosis and deposition of the collagen in the mucosa, accompanied by macrophages within the vessel walls (Fig. 4b).

The Chinese herb containing GF was discontinued from the time of the diagnosis as MP. 3 months after the surgery, the ileostomy was closed, and no anastomotic leakage of the ileo-colostomy was noted. 4 years have passed since the surgery, and there has been no recurrence of colon cancer or MP in her remnant colorectum.

Discussion

MP was first reported in 1991 by Koyama et al. [1], and thus far, only about 100 cases have been reported. These sporadic case reports have been found mainly in Asian countries, especially Japan. MP is believed to be caused by disturbed venous return due to sclerosis in the tributaries of the superior mesenteric vein and induces the development of chronic ischemic changes in the right-side colon. These ischemic changes may induce dysfunctional colon, with symptoms such as abdominal pain, diarrhea, constipation, or ileus [2–5]. The etiology of MP has been unclear, but recently, the relationship between MP and the use of herbal medicines containing GF was reported based on the

Fig. 4 The microscopic findings of the specimen in hematoxylin-eosin stain. **a** The primary tumor was well-differentiated tubular adenocarcinoma invading the muscular propria ($\times 40$). **b** The MP lesion was characterized by marked fibrous thickening of the venous walls

with calcification and marked transmural fibrosis and deposition of the collagen in the mucosa, accompanied by macrophages within the vessel walls ($\times 40$)

results of a large-scale nationwide survey in Japan [6]. The survey showed that 70.4% of MP patients used an herbal medicine containing GF, and 92.6% of them had used it for longer than 5 years. Therefore, the study suggested that the long-term use of herbal medicines containing GF may induce MP. Other studies have also suggested that the main components of GF, geniposide, may play a key role in the development of MP [11, 20–22]. Geniposide is bio-transformed into genipin by β -glucosidase produced by the intestinal microflora at the proximal colon [23]. Genipin is a physiologically active substance, known to be a natural cross-linking reagent and can form intermolecular cross-links in collagen. Hiramatsu et al. suggested that genipin may cause thickening of the collagen fiber in the veins affected by MP [11]. In addition, genipin has been used as a natural dye and can form blue particles on reaction with amino acids and protein, and the dark-purple color of the colon wall of MP patients has been suggested to be due to this reaction [11]. These previous findings suggest that the characteristic dark-purple color, marked transmural fibrosis, and deposition of collagen in the colon wall found in our case were all induced by genipin.

However, the relationship between colorectal cancer and MP was not described in the above studies. Thus far, there have only been rare and sporadic case reports of colorectal cancer coincident with MP [7–15], the majority of which concluded that MP has little association with colorectal cancer. The previously reported cases and our case are summarized in Table 1. Interestingly, 9 of 10 cases (90%) had colon cancer in the right-side colon affected by MP, and 5 of 10 cases (50%) were associated with the use of a Chinese herb containing GF. Proximal shift of colorectal cancer has been observed within the last 6–7 decades, but tumors located proximally to the splenic flexure are now accounting for 30–40% of overall colorectal cancer cases [24]. This summary therefore

suggests that there is indeed a relationship between right-side colon cancer and MP associated with GF.

Although GF is widely used as a traditional Chinese medicine for the treatment of hepatic and inflammatory diseases, one study recently showed that genipin, which is bio-transformed from GF by human intestinal bacteria, poses a genotoxic risk [16], and another study showed that it induces ROS production, COX-2 up-regulation, and Prostaglandin (PG) E₂ production in macrophages [17]. ROS are well known to have potential mutagenic and carcinogenic effects [25], and PGE₂ induced by COX-2 up-regulation can promote cancer progression via the induction of tumor cell proliferation and invasion, the suppression of tumor immunity, and angiogenesis in the tumor microenvironment [26]. Given these present and previous findings, we speculate that genipin, which is a metabolite of geniposide in GF, may be associated with not only the development of MP but also carcinogenesis in the right-side colon. We cannot deny that, in our case, genipin bio-transformed from GF may have induced the ACC in the right-side colon affected by MP associated with genipin. Further studies should be performed to explore the relationship and causality between carcinogenesis and GF.

In conclusion, we herein report a patient with both ACC and MP that may have been caused by the long-term use of a Chinese herb containing GF. We present first speculation that genipin, which is bio-transformed from GF, may be associated with not only the development of MP but also carcinogenesis in the right-side colon based on our case and literature review. Our findings suggest that it is necessary to re-evaluate the safety of GF and gastroenterologists should be aware that GF may induce the risk of not only the development of MP but also carcinogenesis in the proximal colon.

Table 1 Reported cases of colorectal cancer coincident with MP

No	Author	Year	Age	Gender	Herbal medicine containing GF	Location affected by MP	Colon cancer		Gross finding	Histology	Stage	Treatment
							Location	Size (mm)				
1	Shimizu [7]	2000	80	Male	(-)	A ~ T	R	15	type 0-Isp	carcinoma in adenoma	-	Polypectomy
2	Kimura [8]	2003	74	Female	(-)	C ~ D	C	20	-	tub2	-	Total colectomy
3	Ota [9]	2009	73	Female	(-)	C ~ A	A	55	type 2	tub1	T3N0	Right hemicolectomy
4	Yamaoku [10]	2011	82	Male	-	A ~ D	T	80	type 2	tub2	T3N0	Right hemicolectomy
5	Hiramatsu [11]	2012	72	Female	(+)	A	A	-	type 0-Is	-	-	ESD→Right hemicolectomy
6	Komori [12]	2012	57	Male	(+)	C ~ D	A	120	type 2	tub1	T3N0	Subtotal colectomy
7	Omoto [13]	2013	70	Male	-	A ~ D	T	54	type 2	tub1	T3N0	Subtotal colectomy
8	Yamazi [14]	2014	81	Female	(+)	C ~ A	C	20	type 2	tub2	T2N0	Right hemicolectomy
9	Tani [15]	2014	70	Female	(+)	A ~ T	A	-	type 2	tub2	T3N1	Right hemicolectomy
10	Our case	2015	63	Female	(+)	C ~ D	A	90	type 0-IIa	tub1	T2N0	Subtotal colectomy

GF gardenia fruit, MP mesenteric phlebosclerosis, ESD endoscopic submucosal dissection, C cecum, A ascending colon, T transverse colon, D descending colon, R rectum, tub1 well-differentiated tubular adenocarcinoma, tub2 moderately-differentiated tubular adenocarcinoma

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Compliance with ethical standards

Conflict of interest All authors have no conflict of interest to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

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