

A Case of Idiopathic Mesenteric Phlebosclerosis with Progressive Intestinal Necrosis

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The patient was a 39-year-old woman who was referred to our department from her previous doctor with a 2-day history of right abdominal pain. Abdominal computed tomography showed wall thickening associated with calcification in the ascending colon. Contrast enhancement in the same portion of the intestinal wall was rather poor. Fluid accumulation was also seen around the intestine, so emergency surgery was performed under a provisional diagnosis of intestinal necrosis. Intestinal necrosis due to idiopathic mesenteric phlebosclerosis was diagnosed from postoperative histopathological tests. Idiopathic mesenteric phlebosclerosis displays a chronic course and in most cases conservative treatment is indicated. Bowel obstruction is common among patients who require surgical treatment, but rare cases such as the present one are also seen in which intestinal necrosis occurs. In recent years, an association with herbal medicine has been indicated as one potential cause of this disease, and this entity should be kept in mind when patients with acute abdomen and a history of taking herbal medicines are encountered.

Key words: idiopathic mesenteric phlebosclerosis, phlebosclerotic colitis, herbal medicine, intestinal necrosis

INTRODUCTION

Ischemic bowel lesions from phlebosclerosis were first reported by Koyama *et al.* [1] in 1991, and a new disease entity was proposed by Iwashita *et al.* [2] in 1993. In 2000, this condition was named phlebosclerotic colitis by Yao *et al.* [3], but since marked inflammation was not seen histopathologically, Iwashita *et al.* [4] proposed naming this condition idiopathic mesenteric phlebosclerosis in 2003. Ischemic changes are thought to occur in idiopathic mesenteric phlebosclerosis, mainly as circulatory failure in the intestine caused by calcification of veins in the colonic walls and mesentery. Unlike regular ischemic colitis, this a relatively rare disease with a chronic course in most cases. Underlying diseases such as hepatic disease, vasculitis, and diabetes are thought to be contributing causes, but reports [5-7] in recent years have indicated a relationship with herbal medicine. We report a case of idiopathic phlebosclerosis causing progressive intestinal necrosis in a middle-aged woman with a history of taking herbal medicine, and discuss with reference to the literature.

CASE REPORT

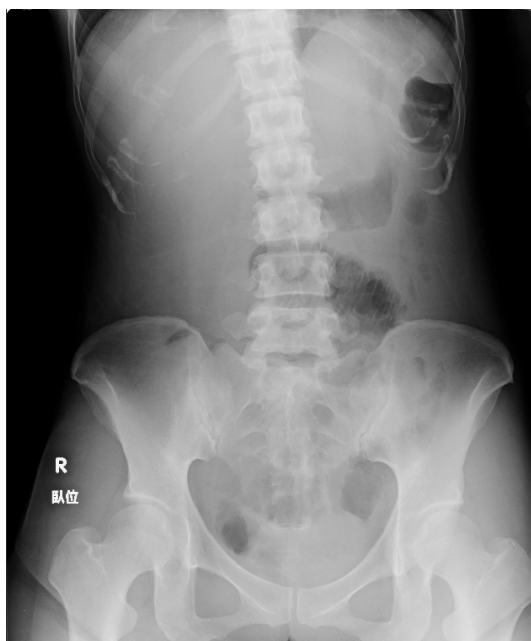
The patient was a 39-year-old woman with a 2-day history of pain in the right abdomen. She was examined by a local doctor who prescribed an intestinal drug, and her course was followed conservatively. However, symptoms persisted and abdominal pain gradually worsened, so she was referred to our hospital. She had a history of atopic dermatitis, and had

taken Shishihakuhto herbal medicine for the previous 4 years. On presentation, physical findings were: body temperature, 39.4°C; blood pressure, 105/64 mmHg; heart rate, 97 beats/min; oxygen saturation, 98%; and respiratory rate, 24 breaths/min. Her abdomen was flat and soft, but with marked tenderness and rebound tenderness in the right abdomen. Muscle guarding was also seen. Blood test results showed: White blood cell count, 29,100/ μ L; C-reactive protein, 29.5 mg/dL; and markedly elevated inflammatory response. Values of CPK and LDH were within normal limit and these data did not increase, so that the findings suggest intestinal necrosis in laboratory data were not observed. No abnormal values were seen in other biochemical or coagulation tests (Table 1). No abnormal gas patterns were seen on plain abdominal radiographs, nor were there any obvious indications of calcification or other patterns (Fig. 1). Abdominal computed tomography (CT) showed distension of the small intestine and accumulation of intestinal contents. Wall thickening with calcification was seen in the ascending colon. While contrast enhancement was seen in the ascending colon wall, the enhancement was rather poor and surrounding accumulation of fluid was seen. However, obvious free air suggests intestinal perforation couldn't be pointed out. (Fig. 2).

Peritonitis from intestinal necrosis was diagnosed based on these findings, and surgery was performed. When the abdominal cavity was first observed laparoscopically, no obvious contamination was seen. However, pus was seen when the greater omentum covering the ascending colon was gently separated, and

Table 1 Laboratory data on admission

Blood examination		Blood chemistry	
WBC	29,100/mm ³	TP	6.4 g/dl
RBC	427 × 10 ⁴ /mm ³	Alb	3.2 g/dl
Hb	13.3 g/dl	T-bil	0.9 mg/dl
Ht	38.20%	AST	17 IU/l
Plt	28.6 × 10 ⁴ /mm ³	ALT	18 IU/l
Coagulation		LDH	165 IU/l
PT%	109%	ALP	115 IU/l
PT-INR	0.97	CPK	25 IU/l
FDP	5 µg/dl	AMY	31 IU/l
D-Dimer	1.3 µg/dl	BUN	16 mg/dl
ATIII-AC	80%	CRN	0.65 mg/dl
Blood Gas Analysis		Na	135 mEq/l
PH	7.459	K	3.2 mEq/l
PaCO ₂	30.0 mmHg	Cl	100 mEq/l
PaO ₂	86.5 mmHg	CRP	29.525 mg/dl
BE	-1.6 mMol/l		
HCO ₃ ⁻	21.0 mMol/l		
Lactate	1.0 mMol/l		
Antibodies		Virus markers	
ANA	< 40	HBsAg	(-)
PF	3.0	HCVAb	(-)
Anti-DNA antibody	2.0	CMV antigenemia	(-)
PR3-ANCA	< 1.0	HSV PCR	(-)
MPO-ANCA	< 1.0		

**Fig. 1** Only intestinal gas is seen on plain abdominal radiography. No calcification is evident.

curdy pus on the serosa of the ascending colon and thinning of the intestinal wall were seen in the same area (Fig. 3). In line with the preoperative diagnosis, necrosis of the ascending colon was diagnosed, but the cause was unclear and conversion to laparotomy was made for the subsequent surgical procedures. Right hemicolectomy was performed. In histopathological

tests of the resected specimens, the gross finding was segmental necrosis of the intestine (Fig. 4a). With hematoxylin and eosin staining, a well-circumscribed area of mucosal necrosis was seen. The same area showed marked thickening of the vein walls and calcification. In addition, the intestinal wall around the mucosal necrosis displayed advanced fibrosis in the

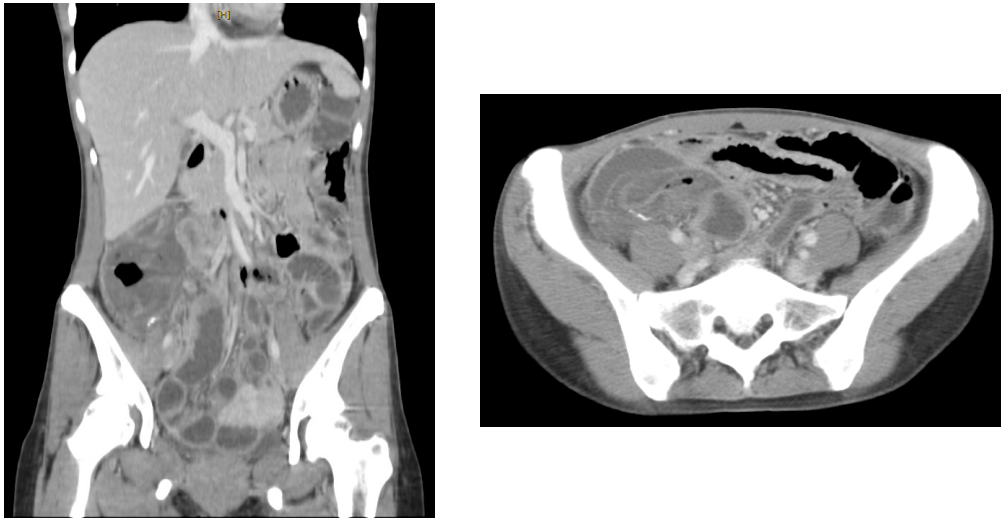


Fig. 2 On abdominal CT, wall thickening with calcification is seen in the ascending colon, contrast enhancement in the intestinal wall is rather poor, and accumulation of fluid in the surroundings is apparent.

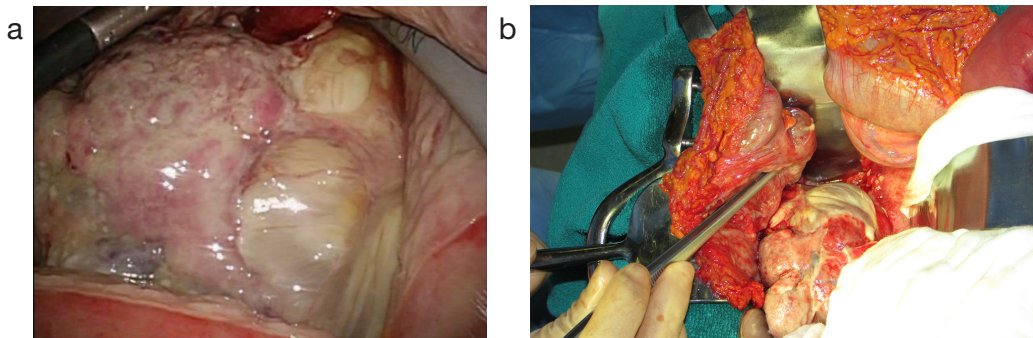


Fig. 3 a) On laparoscopic observation, the wall of the ascending colon is thin, Eiterbelag is seen on the surface, and accumulation of bile can be identified. b) Conversion to laparotomy was performed to allow right hemicolectomy.

submucosa (Fig. 4b). Intestinal necrosis from idiopathic mesenteric phleboscrosis was diagnosed from the above findings.

DISCUSSION

Idiopathic mesenteric phleboscrosis was first reported in 1991 by Koyama *et al.* [1] The disease entity was later proposed by Iwashita *et al.* [2, 3] and Yao *et al.* [4]. Idiopathic mesenteric phleboscrosis is thus a relatively new disease entity, and remains rare. Unlike the traditional ischemic colitis from arterial blood flow obstruction that often occurs in the left colon, chronic ischemic lesions develop in the large intestine from impaired circulation due to hardening of the colon wall and mesenteric veins. In Japan, the prevalence is 0.01 case per 100,000 people. The mean age of patients is 61.8 years (range, 21–88 years) and the pathology shows a slight predilection for women, with a male-to-female ratio of approximately 2: 3. Interestingly, this pathology has only been reported to affect Asians, mostly Japanese [8]. Onset is generally gradual, with cardinal symptoms of abdominal pain, diarrhea, constipation, and abdominal distension [9], although many patients remain asymptomatic [8]. Characteristic radiological findings for this disease include marked

calcification in the venous walls along the straight and marginal arteries from inside the intestinal wall. Many sites of linear and reticular pale calcification are seen, as if following the intestine in the affected area on plain abdominal radiographs. The linear calcifications are more clearly seen on the mesenteric side running in the direction of the short axis of the intestine. On abdominal CT, diffuse wall-thickening in the affected region and a mildly elevated concentration of surrounding subcutaneous adipose tissue are apparent. In the affected intestine, punctate and linear calcifications are apparent within the intestine wall, around the intestine on the mesenteric side, and within the mesentery. Abdominal CT is thought to be better than abdominal radiography for detecting calcifications, and the range of calcification findings is reported to be related to the symptoms [11]. Three-dimensional images in the venous phase on contrast-enhanced CT are useful in understanding the extent of venous wall calcification, the range of diseased blood vessels, circulatory impairment in the superior mesenteric vein, and the development of collateral circulation.

In our patient, calcification was not detected on abdominal radiographs, but abdominal CT revealed punctate and linear calcifications. This was thought to

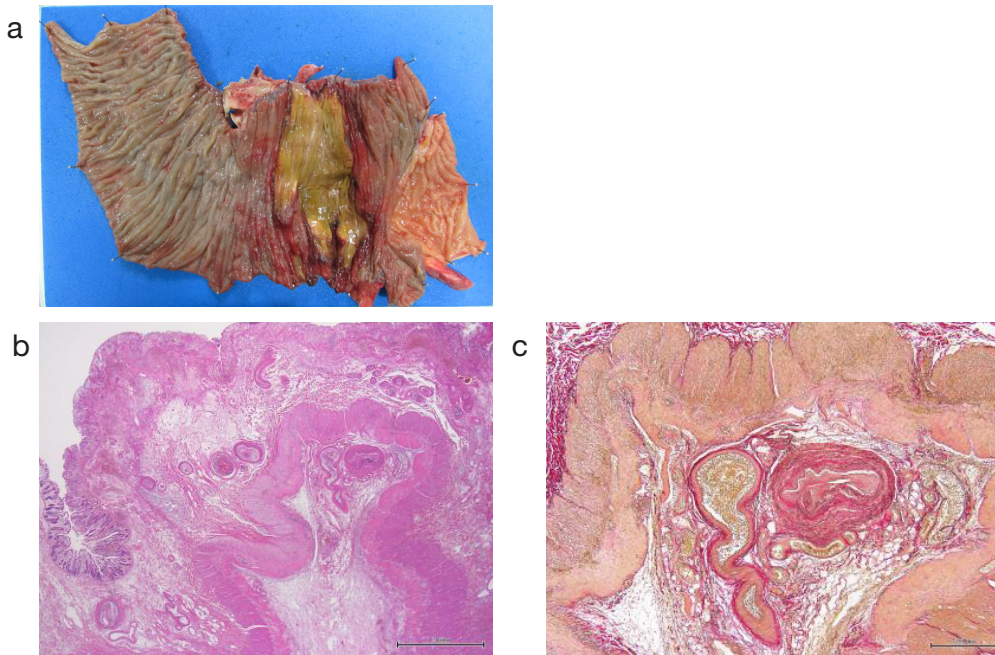


Fig. 4 a) On histopathological examination, the gross finding was segmental necrosis of the intestine. b) HE staining shows a well-circumscribed area of mucosal necrosis. Marked thickening of the vein walls and calcification is also evident in this area. c) With Elastica-van Gieson staining, veins with marked wall thickening and narrowing of the lumen and arteries with thickened walls are seen in the submucosa.

be because the appearance on abdominal radiography is greatly affected by imaging conditions.

In other image findings, the mucosal surface presents a bronze color on lower gastrointestinal endoscopy, because congested venous plexuses in deep areas are visible through the atrophied large intestine mucosa, and diagnosis is sometimes relatively simple with multiple erosion and irregular, shallow ulcerations at the mucosal surface [12, 13]. A case of long-term observation has also been reported in which the patient had no subjective symptoms at all, even as the lesions diagnosed endoscopically gradually progressed [14], but ulceration and intestinal stenosis may also appear and close follow-up is warranted.

Major histological findings include: 1) marked fibrous thickening and calcification of venous walls; 2) advanced fibrosis of the submucosal layer and marked collagen fiber perivascular deposits in the lamina propria; 3) appearance of foam cells in the small vessel walls, mainly in the submucosal layer; 4) thickening and calcification of associated artery walls; and 5) no thrombus formation [15]. Thickening and calcification of the venous walls and fibrosis of the submucosal layer were also seen in our patient, and intestinal necrosis from idiopathic mesenteric phlebosclerosis was diagnosed.

Diabetes, liver disease, genetic factors, and collagen disease are reported to be involved in the etiology of this disease [16], but this is not well understood. However, the first report of a patient taking herbal medicine [5] has been followed by other occasional reports of patients using herbal medicine [6, 7], and this has come to be recognized as a contributing cause. This has been hypothesized to be the result of ingestion of certain toxic or biochemical substances that are absorbed via the venous system from the terminal

ileum and ascending colon, damaging smooth muscle and myofibroblast, which then damage intestinal smooth muscle and surrounding tissue over a long course [5]. In recent years, the kinds and components of herbal medicines taken by patients who develop idiopathic mesenteric phlebosclerosis have been analyzed and some investigations have examined dosing rates of herbal ingredients [17, 18].

According to these investigations, a breakdown of herbal medicine ingredients shows common constituents of gardenia, glycyrrhiza, scutellaria root, and poria sclerotium. A particularly high rate of gardenia has been seen, and is conjectured to be closely related to development of this disease. The main components of the medicinal herbs gardenia, scutellaria root, and glycyrrhiza are the glycosides geniposide, baicalin, and glycyrrhizin, respectively. Glycosides are hydrophilic and are thus not readily absorbed. They stabilize through the binding of sugars, and are resistant to gastric acid. Moreover, their β -glycosidic linkages prevent hydrolyzation with digestive enzymes, allowing these substances to reach the lower intestinal tract. Glycosides that reach the lower intestinal tract are slowly broken down by β -glucosidase from intestinal bacteria, and are thought to exhibit medicinal effects by absorption in the intestine as the respective aglycones [18]. Aglycones are absorbed mainly by the right colon. This means they are absorbed before reaching the distal colon, and the lesions in idiopathic mesenteric phlebosclerosis are suspected to be seen mainly in the right colon.

The shishihakuhto taken by our patient contains gardenia, phellodendron bark, and glycyrrhiza, which may be causes of this disease. Patients in past reports had taken herbal medicine for long periods of 10 years or more, but since cases have also been described in which intestinal necrosis occurred with a relatively

Table 2 Demographics and characteristics of patients who underwent surgery for idiopathic mesenteric phleboscrosis between 1991 and 2015

Demographic/characteristic	Value	%		Value	%
Gender			Operative indication		
Male	18	30.5	ileus	28	47.4
Female	41	69.5	abdominal pain	19	32.2
Age			intestine necrosis	3	5.1
Median (range), years	59 (33-83)		tumor	3	5.1
Chinese herbal use			perforation	3	5.1
Yes	26	44.1	bloody bowel discharge	2	3.3
No	33	55.9	fistulation due to intestinal Bechet	1	1.6
kamishoyosan	7	26.9	Surgery		
orengedokuto	5	19.2	subtotal colectomy	37	62.7
shishihakuhito	3	11.5	right hemicolectomy	15	25.4
senna	2	7.6	extended right hemicolectomy	2	3.3
juzentaihoto	1	3.8	total colectomy	2	3.3
daikennchuto	1	3.8	ileocecal resection	1	1.6
daiobotanpito	1	3.8	appendectomy	1	1.6
bofutsushosan	1	3.8	drainage	1	1.6
rikkunshito	1	3.8	Approach		
tokakujokito	1	3.8	Open	46	77.9
anchusan	1	3.8	Laparoscopic	13	22.1
shiniseihaito	1	3.8			
unkown	7	26.9			
Administration period					
Median (range), years	16 (3-25)				
Location of lesions					
Limited to right colon (cecum and ascending colon)	4	6.7			
Continuous from cecum extended to transverse colon	34	57.6			
Continuous from cecum extended to left colon (descending and sigmoid colon)	19	32.2			
Continuous from cecum extended to rectum	2	3.3			

short history of taking herbal medicine, and our patient had taken these medicines for four years, regular abdominal radiography and colonoscopy may need to be considered even without symptoms in patients taking herbal medicine.

However, not all individuals taking herbal medicine develop idiopathic mesenteric phleboscrosis. Since intestinal bacteria contribute to the medicinal effects of herbal medicine individual differences exist in intestinal flora, individual differences are also reported to be likely in metabolism and medicinal efficacy [19]. Furthermore, some patients with idiopathic mesenteric phleboscrosis have no history of taking herbal medicine and elucidation of the pathology underlying this disease will require accumulation of more cases in the future.

Reported treatments include anticoagulants [20] and aminosalicylic acid preparations [21], but a slow course

is a characteristic of this disease when symptoms are limited to mild gastrointestinal symptoms. Treatment is thus principally conservative, and patients taking herbal medicines should first be discontinued from those agents and the course followed. However, even when herbal medicines are discontinued, symptoms progress and intestinal stenosis occurs in some patients [22-24], so close follow-up is warranted. Surgical treatment may be needed in cases showing no response to conservative treatment.

Surgery for this condition has been reported for 59 patients, including the present patient. The patient who had taken herbal medicine was 44.1%, and the patients who were taking shishihakuhito were 2 patients except for present patient. A taking period was 10 [22] and 20 [25] years respectively (Table 2). The reason for surgery in such cases is often bowel obstruction from intestinal stenosis, but caution is needed, as cases such

as the present show intestinal necrosis. With surgical treatment in cases of bowel obstruction, affected areas are not always limited to the right colon by the time of surgery is performed. In many cases, the condition has progressed to the transverse and descending colon. As a result, the length of resected colon tends to become longer, such as with subtotal colectomy. When determining the range of resection, the diseased intestine might be appropriately resected by looking not only at the color of the serosa and intestinal wall thickening findings intraoperatively, but also by checking the range of calcification preoperatively on abdominal CT when possible, checking color changes in the mucosal surface and the range of edema, stenosis, erosions, and ulcerations with colonoscopy, and marking the planned resection portion with India ink or similar before surgery.

Occasional reports on laparoscopic surgery for bowel obstruction in idiopathic mesenteric phlebosclerosis have recently been seen [26, 27]. Intestinal mobilization can be performed while clearly checking the color of the intestine laparoscopically, and laparoscopic colectomy, in which dissection and anastomosis can be performed while visually examining the diseased intestine or markings again directly by lifting the intestine from a small incision, is beneficial in benign diseases such as in the present case.

CONCLUSION

We treated a patient with intestinal necrosis from idiopathic mesenteric phlebosclerosis. The etiology of this disease is not yet well understood, but reports occasionally suggest a relationship with herbal medicine, as in this case, and caution is needed regarding long-term use of herbal medicines. The course of this disease is often chronic, and patients such as the present one can develop intestinal necrosis. This disease should be considered in cases of acute abdomen.

REFERENCES

- 1) Koyama N, Koyama H, Hanajima T, Matsubara N, Shimada T, Fujisaki J, *et al.* Chronic Ischemic Colitis Causing Stenosis, Report of a case. *Stomach & Intestine* 1991; 26: 450-460.
- 2) Iwashita A, Takemura S, Yamada Y, Hasegawa S, Yao T, Utsunomiya T, *et al.* Pathomorphologic Study on Ischemic Lesions of the Small and Large Intestine. *Stomach & Intestine* 1993; 28: 927-941.
- 3) Yao T, Iwashita A, Hoashi T, Matsui T, Sakurai T, Arima S, *et al.* Phlebosclerotic colitis: value of radiography in diagnosis-report of three cases. *Radiology* 2000; 214: 188-192.
- 4) Iwashita A, Yao T, Schlemper RJ, Kuwano Y, Yao T, Iida M, *et al.* Mesenteric phlebosclerosis: a new disease entity causing ischemic colitis. *Dis Colon Rectum* 2003; 46: 209-220.
- 5) Chang K.M. New Histologic Findings in Idiopathic Mesenteric Phlebosclerosis: clues to its pathogenesis and etiology-probably ingested toxic agent-related. *J chin Med Assoc* 2007; 70: 227-235.
- 6) Yoshii S, Tsukagoshi H, Kusumi T, Suzuki Y. Idiopathic Mesenteric Phlebosclerosis: Long-term Use of the Chinese Herbs-Report of Four Cases. *J Jpn Soc Coloproctol* 2010; 63: 389-395.
- 7) Ohtsu K, Mastui T, Nishimura T, Hirai F, Yorioka M, Sakurai T, *et al.* Mesenteric Phlebosclerosis-Long-term Clinical Course and Relationship with the Chinese Herbal Medicine. *Stomach & Intestine* 2012; 65: 369-375.
- 8) Yoshinaga S, Nakamura K, Harada N, Yao T. Clinical Features of Idiopathic Mesenteric Phlebosclerosis. *Stomach & Intestine* 2009; 44: 163-169.
- 9) Iwashita A. Idiopathic mesenteric phlebosclerosis. *Stomach & Intestine* 2009; 44: 135-136.
- 10) Hirata I. Radiologic Diagnosis of Idiopathic Mesenteric Phlebosclerosis. *Stomach & Intestine* 2009; 44: 170-181.
- 11) Yen TS, Lin CA, Chiu NC, Chiou YY, Chou YH, Chang CY. Relationship between severity of venous calcifications and symptoms of phlebosclerotic colitis. *World J Gastroenterol* 2015; 21: 8148-8155.
- 12) Noritake H, Yamada M, Takehira Y, Kageyama F, Yoshii S, Iwaoka Y, *et al.* A Case of Phlebosclerotic Colitis Involving the Entire Colon. *Gastroenterol Endosc* 2008; 50: 1115-1122.
- 13) Yasuda A, Ishizuka D, Hori T, Katashima T, Kaneda S, Shimizu S, *et al.* Ischemic Intestinal Lesion Caused by Phlebosclerosis, Report of a Case. *Prog Dig Endosc* 1999; 54: 73-76.
- 14) Shimizu K, Shimizu S, Koga H, Ishida H, Minami T, Mihara M, *et al.* Serial Endoscopic Changes in Mesenteric Phlebosclerosis, Report of a Case and a Review of the Literature. *Stomach & Intestine* 2009; 44: 259-266.
- 15) Ikeda K, Iwashita A, Haraoka K, Ota A, Oshige K, Tanabe H, *et al.* Pathology of Idiopathic Mesenteric Phlebosclerosis. *Stomach & Intestine* 2009; 44: 138-152.
- 16) Kitamura T, Kubo M, Nakanishi T, Fushimi H, Yoshikawa K, Taenaka N, *et al.* Phlebosclerosis of the colon with positive anti-centromere antibody. *Intern Med* 1999; 38: 416-421.
- 17) Hiramatsu K, Sakata H, Horita Y, Orita N, Kida A, Mizukami A, *et al.* Mesenteric phlebosclerosis associated with long-term oral intake of geniposide, an ingredient of herbal medicine. *Aliment Pharmacol Ther* 2012; 36: 575-586.
- 18) Ohtsu K, Matsui T, Nishimura T, Hirai F, Ikeda K, Iwashita A, *et al.* Association between mesenteric phlebosclerosis and Chinese herbal medicine intake. *Jpn. j. gastroenterology* 2014; 111: 61-68.
- 19) Hattori M. Intestinal Bacteria Play a significant Role in the Medicinal Effects of Kampo Medicines. *Journal of Intestinal Microbiology* 2012; 26: 159-169.
- 20) Ikehata A, Hiwatashi N, Kawarada H, Yamazaki H, Ito K, Kinouchi Y, *et al.* Chronic Ischemic Colitis Associated with Marked Calcifications of the Mesenteric Vessels -Report of Two Cases-. *Dig Endosc* 1994; 6: 355-364.
- 21) Yasuda A, Ishizuka D, Hori T, Katakami T, Kaneda S, Shimizu S, *et al.* Ischemic Intestinal Lesion Caused by Phlebosclerosis, Report of a Case. *Prog Dig Endosc* 1999; 54: 73-76.
- 22) Ohe R, Kabasawa T, Suto A, Yang S, Kato T, Osakabe M, *et al.* Subtotal colectomy for idiopathic mesenteric phlebosclerosis: a case report. *Jpn J Diagn Pathol* 2014; 31: 223-228.
- 23) Guo F, Zhou YF, Zhang F, Yuan F, Yuan YZ, Yao WY. Idiopathic mesenteric phlebosclerosis associated with long-term use of medical liquor: Two case reports and literature review. *World J Gastroenterol* 2014; 20: 5561-5566.
- 24) Fang YL, Hsu HC, Chou YH, Wu CC, Chou YY. Phlebosclerotic colitis: A case report and review of the literature. *Exp Ther Med* 2014; 7: 583-586.
- 25) Takeda K, Nakagawa T, Yamada T, Konishi K, Okuyama M, Nishijima J. A case report of idiopathic mesenteric phlebosclerosis associated with long-term use of a Chinese medicine. *J Jpn Surg Assoc* 2015; 76: 1314-1319.
- 26) Washio M, Fukunaga M, Nagakari K, Katsuno G, Hashizume A, Yamamoto S. A case of phlebosclerotic colitis treated by laparoscopic surgery. *J Jpn Surg Assoc* 2012; 73: 80-86.
- 27) Koinuma K, Horie H, Shimizu T, Kumano H, Miyakura Y, Yasuda Y. A patient with idiopathic mesenteric phlebosclerosis treated with laparoscopic-assisted colectomy. *J. Jpn. Soc. Endosc. Surg.* 2013; 18: 73-78.