New Histologic Findings in Idiopathic Mesenteric Phlebosclerosis: Clues to Its Pathogenesis and Etiology—Probably Ingested Toxic Agent-related

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Background: Idiopathic mesenteric phlebosclerosis (IMP) is a recently known and rare disease entity, which is a member of non-thrombotic, non-inflammatory stenosis or occlusion of the mesenteric veins. In spite of the unique histopathology and particular location, the cause and pathogenesis of IMP remain unknown. The aim of this brief study was to propose a pathogenesis and possible etiology based on the reviewed clinical data and some newly discovered pathologic findings in several recent cases in our and other hospitals.

Methods: The clinical data of 5 patients were collected, with detailed tracing of past history, drug use and dietary habit. The histologic sections were reviewed in detail, with additional histochemical stains and immunohistochemical stains in 4 available cases.

Results: The most important of our findings other than the previously described typical features was a unique type of coagulative necrosis, which we call mummification, involving not only the muscular coat of veins in early and late phases but also the subsequent hyperplastic myointima in veins, portion of the media of arteries closely neighboring the sclerotic vein, a zone of muscular wall of the colon around the passing sclerotic veins and the inner zone of muscular wall of the colon, and accompanied by fibrosis/sclerosis and then calcification in the damaged tissues. Two of our patients were a couple who had been taking Chinese herbs regularly.

Conclusion: A pathogenesis is suggested for at least a subgroup of cases of IMP: the disease is initiated by a slow but longstanding direct hypoxic injury to the venous muscular layer, which leads to gradual mummification and then sclerosis and calcification of the venous muscle. This is followed by the repeated same damage of the subsequent reactively hyperplastic myointima in the veins, and these changes finally result in gradual venous occlusion. Certain toxins or biochemicals, probably existing in the frequently ingested contents and absorbed to the venous return, may play the most important role in this damage. However, analysis of more cases is required to support the proposal, and if such support is found, the toxic agents remain to be clarified via further laboratory investigations. [*J Chin Med Assoc* 2007;70(6):227–235]

Key Words: calcification, colon, mummification, myointimal hyperplasia, phlebosclerosis, toxin, veno-occlusive disease

Introduction

Idiopathic mesenteric phlebosclerosis (IMP), a recently known and rare disease entity causing chronic mesenteric ischemia (mainly ischemic colitis), is a member of non-thrombotic, non-inflammatory stenosis or occlusion of the mesenteric veins. In 1989, Iwashita reported the first peculiar patient, and this disease was reported only from Japan since then until 2003.[1–5] In Taiwan, a few cases were presented for the first time at an annual meeting of colorectal surgeons in 2003 (but not published). The usual/typical clinicopathologic features of IMP are summarized in Table 1. IMP chiefly involves the right colon in a continuous distribution and, sometimes, the distal colon and terminal ileum, without rectal involvement or skip lesions. The histologic hallmark is marked fibrous mural thickening/sclerosis of the venous walls, usually circumferential but occasionally eccentric. It is frequently accompanied by calcifications (sometimes also with ossification), but without

Table 1. Common/typical clinical and pathologic features of idiopathic mesenteric phlebosclerosis*

Age range	36–77 yr
Gender	Slight female predominance
Common chronic presenting symptoms; duration	Abdominal pain (mostly right lower quadrant), recurrent diarrhea, nausea, vomiting; 2 mo – 20 yr
Other or possible acute symptoms	Constipation, tarry/bloody stool, fullness sensation; abdominal distension, ileus symptoms, perforation (rare)
Abdominal plain film	Linear/threadlike calcification (in all cases) in right hemicolon and maybe to proximal part of the left colon
Other imaging findings in the lesional segment (barium enema, computed tomography and angiography)	Stenosis (frequently with thumb printing) and luminal narrowing of colon, tortuosity of veins along the vasa recta with pulling at late venous phase, mild narrowing of the marginal arteries and tortuosity of the vasa recta
Endoscopic findings	Edematous, hyperemic to dark-colored nodular colon mucosa and multiple nonspecific ulcers (irregular but not longitudinal)
Involved segments	Cecum to transverse colon (from terminal ileum and/or to sigmoid colon)
Gross findings	Dark purple or brown discoloration of colonic luminal surface/wall, swelling and disappearance of plicae semilunares coli, marked thickening of the colonic wall, ulcers
Histologic hallmark	Marked fibrosis/sclerosis and thickening of the venous walls (with calcification in nearly all cases)
Associated histologic changes (as chronic ischemic colitis)	Atrophy, congestion, hemorrhage and fibrosis of the mucosa, submucosal fibrosis, and thickening and fibrosis of the muscularis propria
Possible changes in arteries	Mild to moderate fibromuscular thickening of the intima (eccentric or circumferential), focal mild calcification and mild hypertrophy of media

Summarized from data in the literature.

inflammatory infiltration in the venous walls. The venous change occurs from the submucosal venules nearly to the SMV trunk and causes narrowing to total obliteration of the venous lumens. The colon wall has the features of consequent chronic ischemic colitis. The changes in the colon wall and veins are more severe over the proximal segment. Neither venous thrombosis (even in the SMV trunk) nor amyloid deposition is found in the lesions. The changes in the accompanying arteries are occasional, focal and mild, and they do not correspond to the severe colonic damage, but seem secondary to the increased peripheral resistance.

All the reported cases of IMP have pathology different from that of the other rare causes of nonthrombotic mesenteric venous occlusion, such as allergic granulomatous angiitis (Churg-Strauss), venulitis associated with systemic lupus erythematosus (that with arteritis in SLE), Behcet's disease, Buerger's disease (thromboangiitis obliterans), enterocolic lymphocytic phlebitis, idiopathic myointimal hyperplasia of the mesenteric veins (IMHMV) and mesenteric inflammatory veno-occlusive disease (MIVOD).[6–9] In spite of the clearly known unique clinicopathologic settings, however, the pathogenesis of IMP has not been well established and the cause remains unknown. We recently encountered 2 patients, a couple, with typical features of IMP, and discovered some special features not described in the literature. A detailed review of several other typical cases was made and, based on some common new findings in these cases, we speculated one possible pathogenesis and etiology.

Methods

The clinical data of 5 patients (2 in our hospital and 3 from others) were collected and analyzed, together with tracing of past history, drug use and dietary habit. The histologic sections (hematoxylin and eosin [H&E] stain) were reviewed in detail, with additional histochemical stains (Elastin von Gieson [EVG] stain for elastic fibers and Masson's trichrome stain for collagen and muscle fibers) and immunohistochemical stains from 4 available cases, including anti-human smooth muscle actin and anti-human collagen IV (clone 1A4 and clone CIV 22, respectively, from Dakocytomation Denmark A/S).

Results

The clinical data of these 5 patients with IMP are summarized in Table 2. They are not much different from those described in the literature, but some interesting

Table 2. Clinical data of our 5 patients with idiopathic mesenteric phlebosclerosis (IMP)

Case	Age (yr)/ Sex	Duration of herb ingestion	Past history	Presenting chronic symptoms (and duration)*	Site	Preoperative diagnosis	Treatment
1	46/F[†]	>10 yr	Appendectomy, HBV healthy carrier	Abdominal pain, recurrent diarrhea, nausea and occasional vomiting (6 mo)[†]	C-S	Crohn's disease	Subtotal colectomy (dead on 3rd day after surgery)
2	47/M[†]	>10 yr	Nil	Intermittent postprandial fullness and dull pain (3 yr)	ND	—	Conservative (half-year follow-up)
3	33/M	>10 yr	Abdominal blunt injury 6 yr previously	Right lower abdominal pain, recurrent diarrhea (6 mo)[†]	C-T	Acute appendicitis	Subtotal colectomy
4	53/M	4–5 yr	Blunt injury over left upper quadrant 5 yr previously	Lower abdominal pain (1.5 yr)[†]	I-S	IMP	Subtotal colectomy
5	52/F	>20 yr	Mild chronic glomerulonephritis (2 yr)	Diarrhea, occasional vomiting (3 yr)[†]	I-S	IMP	Subtotal colectomy

*Duration of chronic symptoms until histopathologic diagnosis; [†]a couple; [‡]see text for the acute symptoms. HBV = hepatitis B virus; C = cecum; S = sigmoid colon; ND = not documented; T = transverse colon; I = terminal ileum.

Figure 1. Abdominal plain film of Case 2 shows typical linear calcifications (arrows) along the right colon to descending colon, thickened colon wall and stenosis indicated by gas in the transverse colon.

observations are worth mentioning. The patients' ages ranged from 33 to 53 years old (46.2 years on average, which is much lower than that of reported series). Case 1, the wife of the couple, visited our outpatient gastrointestinal department regularly for 3 years and was admitted once, but was not diagnosed with IMP until colectomy during the last admission. She had acute onset of shortness of breath following several days of progressive abdominal pain and distension and lower leg edema besides the other chronic symptoms, and received emergent surgery for acute peritonitis due to suspected colon perforation. She died of septic shock on the 3rd postoperative day. Her husband, Case 2, came to our hospital 1 month after her death, complaining of the listed chronic discomforts. He was diagnosed to have the same disease based on the clinical history and typical linear calcifications on abdominal plain film in the later (Figure 1), and received conservative treatment after a colonoscopic exam with biopsy to confirm and evaluate the severity of the colon lesion. He has remained stable till now. Case 3, the youngest patient among the known cases, developed acute right lower quadrant pain, nausea, bloody diarrhea and fever for 2 days, and was given an emergent appendectomy under the impression of acute appendicitis, which turned to subtotal colectomy during the operation. The diagnosis of IMP was not given by the original corresponding pathologist, who
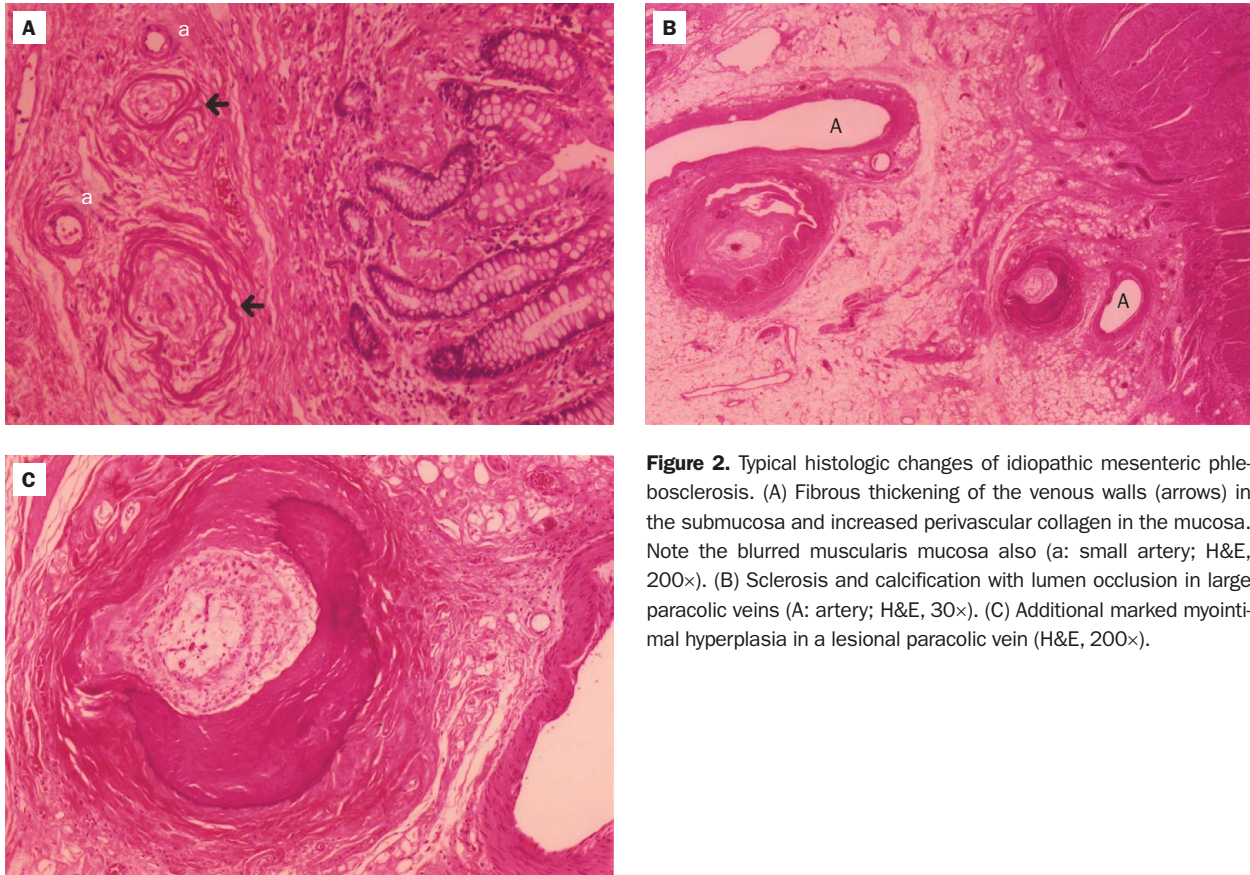
Figure 2. Typical histologic changes of idiopathic mesenteric phlebosclerosis. (A) Fibrous thickening of the venous walls (arrows) in the submucosa and increased perivascular collagen in the mucosa. Note the blurred muscularis mucosa also (a: small artery; H&E, 200×). (B) Sclerosis and calcification with lumen occlusion in large paracolic veins (A: artery; H&E, 30×). (C) Additional marked myointimal hyperplasia in a lesional paracolic vein (H&E, 200×).

described "atherosclerosis" for the fibrotic vessels. Cases 4 and 5, the 2 patients from another hospital, received operation for acute ileus and under the clinical diagnosis of IMP by 2 alert surgeons aware of the typical features on plain film. In fact, all our patients' abdominal plain films showed the typical linear calcifications along the right colon and occasionally, in a lower intensity, to the sigmoid colon. None of these 5 patients had other particular gastrointestinal tract disorders, liver cirrhosis, autoimmune diseases, systemic vascular diseases or coagulative disorders. However, every one had ingested certain kinds of Chinese herbs for a long time, ranging from several to more than 10 years (the couple with the same duration and contents). The ingredients of these herbs were complex and not clearly known, and were not analyzed in our study. The dietary habit of each patient was unremarkable. The surviving 3 post-colectomized patients recovered fairly well with no or much milder discomfort.

The resected intestines had typical and common gross and microscopic appearances of IMP, i.e. those of subacute or chronic ischemic colitis caused by venous occlusion with marked fibrous mural thickening/ sclerosis/calcification of the venous walls (Figure 2A & 2B), while without venous thrombosis or amyloid deposition. Some deep fissures in the ulcer base with microperforations of the colon wall and a pericolic abscess were present in cases 1 and 5, respectively. The vascular changes were milder in the distal colon. There was only seldom mild neutrophilic infiltration in the veins just beneath the ulcers. As in the case reported by Iwashita, collection of foamy macrophages within the walls of some vessels of both arterial and venous types were occasionally seen, and rarely noticed was foreign body-type reaction to degraded calcified part of the lesional veins. The non-ulcerated colon mucosa might not be so atrophic as that in usual ischemic colitis, but mildly thickened due to marked congestion and increase of collagen in the lamina propria.

In addition to the findings being not very different from those described in the literature, under detailed review, we found that many lesional veins in all our patients had various degrees of myointimal hyperplasia (either eccentric or circumferential; Figure 2C), which was absent in the reported cases by Iwashita. Furthermore, in all the involved veins of our cases, a unique type of coagulative necrosis was found in their muscular coats (Figure 3). The necrotic muscle fibers became pink ghost shadows with absence of nuclear staining while, even in the late severely involved stage, without
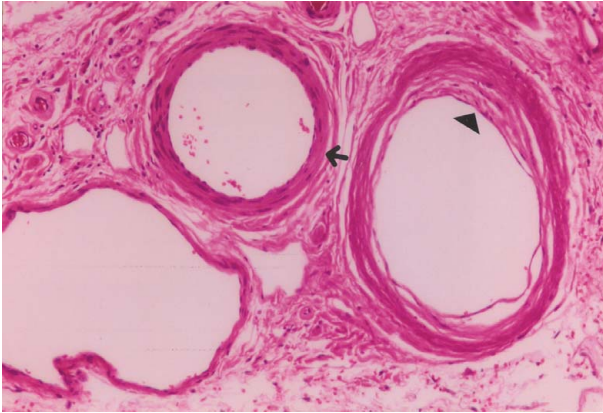
Figure 3. A unique type of necrosis: mummification of the muscular coat of an early involved vein (right) in the distal colon. Note the focal early mild myointimal hyperplasia (arrowhead) and compare with healthy walls of the adjacent artery, non-involved vein and lymphatics. A small portion of the artery actually already has early mummification (arrow) (H&E, 200×).

Figure 4. Mummification of the thick hyperplastic myointima (arrows) in a large vein. The mummified original muscular coat of the vein is below (arrowheads) (H&E, 500×).

fragmentation and removal as that following classical coagulative necrosis. Features of apoptosis were not found either. The necrosis was not readily visible in the small veins under routine H&E stain, but could be better recognized in the larger veins with thick muscular coat (as well as in some tissues of other structures stated below). We called this type of necrosis "mummification" (see discussion), which was easily overshadowed by fibrosis/sclerosis and dystrophic calcification developing subsequently. Indeed, this mummification was also found to always involve the following: (1) the hyperplastic myointima in lesional veins (mainly its outer zone); (2) the media of the corresponding artery just in its portion closely neighboring the sclerotic vein; (3) a zone of muscularis propria of colon around the passing sclerotic vein; and (4) the inner zone of muscularis propria of the colon (Figures 4–6). Sclerosis also occurred in these mummified tissues, especially invariably in the hyperplastic myointima of abnormal veins, with frequently accompanying calcification. The existence of these new and other detailed findings are summarized in Table 3. It is noteworthy that the mummified, sclerotic and calcified parts of hyperplastic myointima usually could not be readily distinguished from the changed original muscular coat of the vein (and might be fused with this), though clefts probably caused during tissue processing could be sometimes seen between these 2 layers. In addition, the original muscular coat of veins was frequently compressed and attenuated by the sclerotic/calcified myointima. In our experience, EVG stain might help, not only for recognizing the venous or arterial nature of the sclerotic-calcified vessels, but also to distinguish the hyperplastic
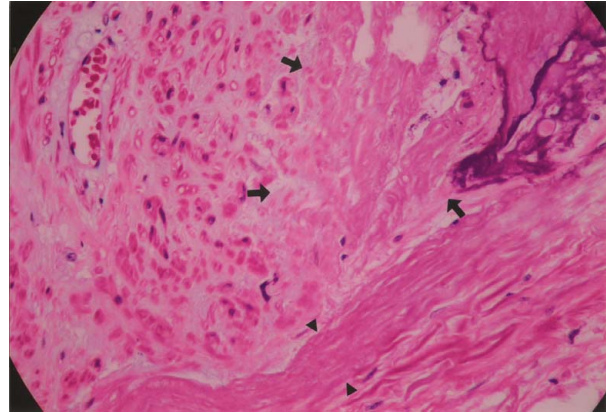
myointima from the original muscular coat of vein, due to lack/scarcity and fair preservation of fine elastic fibers in the former and in the latter of larger veins even mummified, respectively. Masson's trichrome stain and immunohistochemical stain for smooth muscle actin could also help in recognizing the mummified tissues, as blue staining under the former and markedly decreased or negative staining in the dead muscle fibers under the latter (Figure 6B). The immunohistochemical stain for collagen IV revealed that the matrix in the sclerosis had paucity of collagen IV.

Finally, 2 patients' intestines had a "watershed" at the ileocecal valve, i.e. a very narrow separating zone with involved veins at the colonic side and non-involved veins at the ileal side (Figure 7). The veins in the appendices of cases 3 and 4 were also free of abnormal changes, even when the veins in the adjacent terminal ileum of case 4 were sclerotic. Lymphatic vessels were not involved.

Discussion

Venous occlusion is less frequently the cause of occlusive mesenteric ischemia, and usually results from thrombosis. IMP is one of the rare causes of mesenteric venous occlusion, and its clinical presentations are usually gradual and chronic, different from those of acute mesenteric venous thrombosis, while similar to chronic inflammatory bowel disease (IBD). It is quite different from Crohn's disease, ulcerative colitis, ischemic colitis or other colon diseases in radiologic and histopathologic aspects. However, unawareness of the characteristic calcifications on plain film, limited endoscopic exam over the less involved distal segment or biopsy only at the nonspecific ulcers or congested mucosa
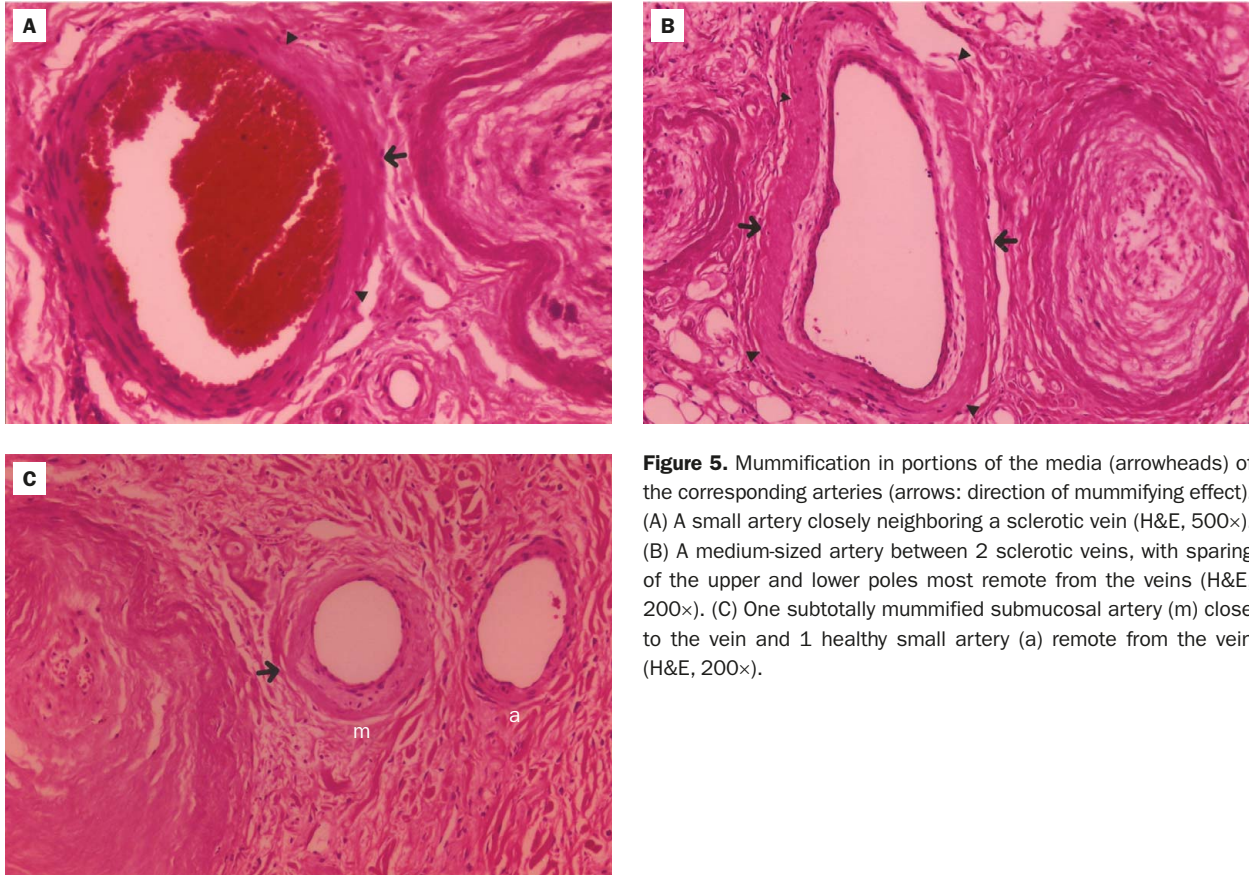
Figure 5. Mummification in portions of the media (arrowheads) of the corresponding arteries (arrows: direction of mummifying effect). (A) A small artery closely neighboring a sclerotic vein (H&E, 500×). (B) A medium-sized artery between 2 sclerotic veins, with sparing of the upper and lower poles most remote from the veins (H&E, 200×). (C) One subtotally mummified submucosal artery (m) close to the vein and 1 healthy small artery (a) remote from the vein (H&E, 200×).

might lead to a misdiagnosis. A cursory examination of sections only stained with H&E stain might also lead to an erroneous recognition of calcified vessels as arteries (such as in Case 3). Therefore, IMP may be under-diagnosed in routine gastroenterology and pathology practice.

As for the differential diagnoses, and maybe for the pathophysiology, 2 other entities in the rare causes of mesenteric venous occlusion should be mentioned—IMHMV and MIVOD.

IMHMV is a poorly understood disease occurring in and confined to the rectosigmoid colon of predominantly young, previously healthy male patients. Its clinical course usually leads to impression of IBD, while mucosal biopsy findings are incompatible with IBD. The typical histologic finding is extensive myointimal hyperplasia of mesenteric veins without vasculitis or arterial involvement, whereas the vessel walls external to the thickened intima appear normal. An acquired segmental arteriovenous fistulization is proposed as the cause. Except for the myointimal hyperplasia and secondary ischemia of bowel, the other features of IMHMV are quite different from those of IMP. MIVOD, also unknown in etiology, is an unusual isolated vasculitis of the mesenteric veins and their

intramural tributaries. The vasculitis may be lymphocytic, necrotizing, granulomatous, or mixed, and thrombosis is invariably present—this may overshadow the inflammatory components. The myointimal hyperplasia and occlusive phlebosclerosis are considered to represent organized thrombi in the later.[9] The typical inflammatory and thrombotic features were not found in our and other reported cases of IMP.

As for the pathogenesis of IMP, the hallmark of histologic changes—fibrosis of venous walls—should be discussed in advance. Iwashita stated in his report that the changes in venous wall, even in the very early stage, consisted merely of fibrous thickening/deposits of collagen fibers and calcium deposits in the "intima". Other reporters also only briefly described the fibrosis and calcification of the lesional veins, but the details and the preceding events were not mentioned. However, fibrosis/calcification is well known to be the later change of many disease processes such as degeneration and necrosis. In routine practice, we can see direct fibrosis/hyalinization in benign ischemic infarction in many uterine leiomyomas. As per Kloner's descriptive term for the infarcted myocardium which did not undergo disintegration in their experiment,[10] we therefore also adopt the term *mummification* for the
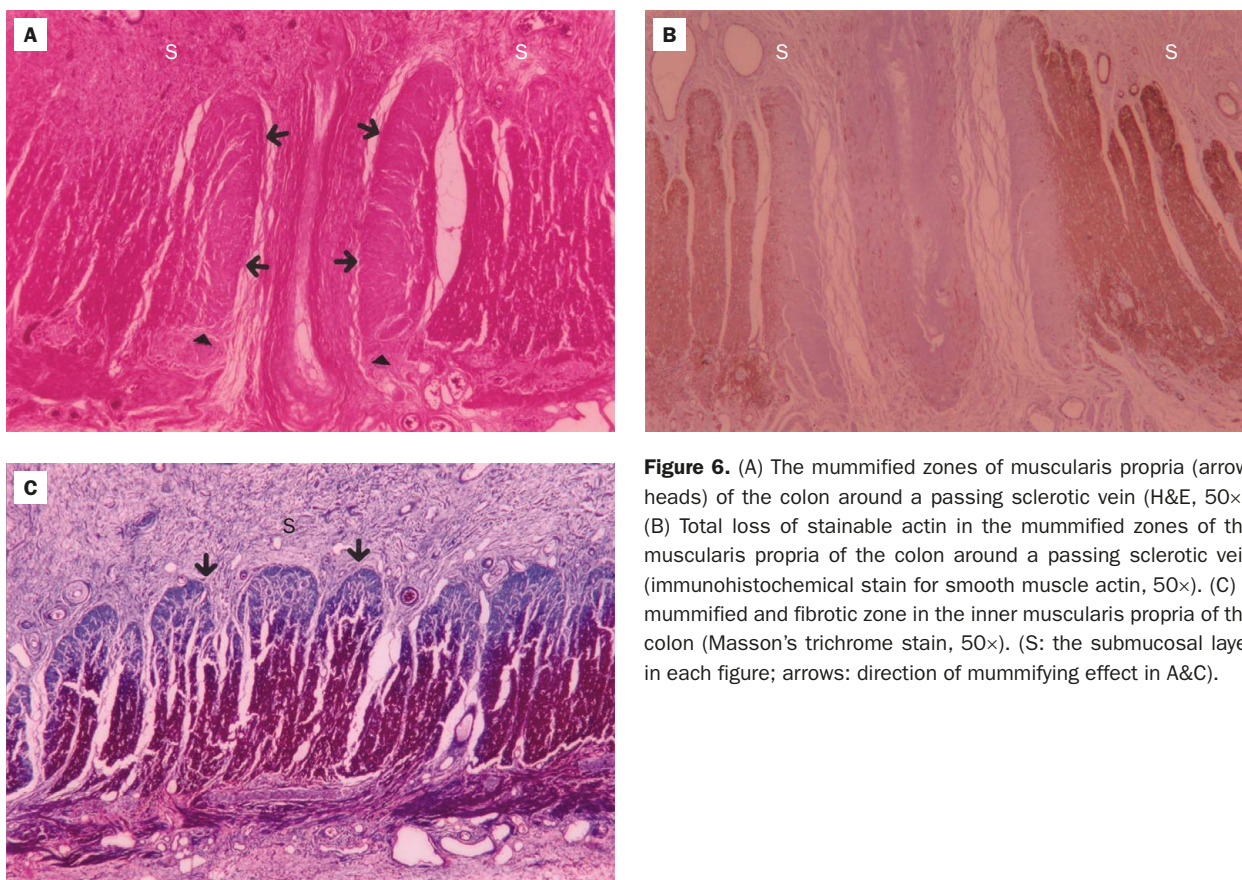
Figure 6. (A) The mummified zones of muscularis propria (arrowheads) of the colon around a passing sclerotic vein (H&E, 50×). (B) Total loss of stainable actin in the mummified zones of the muscularis propria of the colon around a passing sclerotic vein (immunohistochemical stain for smooth muscle actin, 50×). (C) A mummified and fibrotic zone in the inner muscularis propria of the colon (Masson's trichrome stain, 50×). (S: the submucosal layer in each figure; arrows: direction of mummifying effect in A&C).

Table 3. Detailed/new histologic findings of idiopathic mesenteric phlebosclerosis in our patients

Findings	Case 1	Case 2	Case 3	Case 4	Case 5
Necrosis/mummification of muscular coat of veins*	Present	NA	Present	Present	Present
Hyperplastic myointima of vein	Present	NA	Present	Present	Present
Mummification/sclerosis of hyperplastic myointima of vein*	Present	NA	Present	Present	Present
Partial mummification of media of artery neighboring to the sclerotic vein*	Present	NA	Present	Present	Present
Mummified zone of muscularis propria of colon around a passing sclerotic vein*	Present	NA	Present	Present	Present
Mummification of inner zone of muscularis propria of colon*	Marked	NA	Mild	Marked	Marked
Ileocecal valve as watershed*	Present	NA	Present	Absent	Absent
Involvement of veins in appendix*	NA	NA	Absent	Absent	NA
Phlebosclerosis in terminal ileum	Absent	NA	Absent	Mild	Marked

*Not yet described in literature (please see text). NA = not available.

similar and unique type of necrosis of the venous muscular coat in our cases, and consider it to be the preceding event. Additionally, in contrast to Iwashita's report, myointimal hyperplasia was noticed in the lesional veins in all of our cases. However, this change is known to occur in a variety of conditions, such as those mentioned above, grafted vessels and idiopathic portal hypertension and, interestingly, in our cases, it occurred in the veins already with mummified muscular coat rather than those with still viable wall. We therefore consider that the myointimal hyperplasia was a common secondary reactive change to such a necrotizing insult on blood vessels, but its presence did accelerate the vascular occlusion.

Based on our new findings, it seems reasonable that the change begins as a slow but longstanding and direct hypoxic injury to the venous muscular layer, which leads to gradual mummification and then sclerosis and
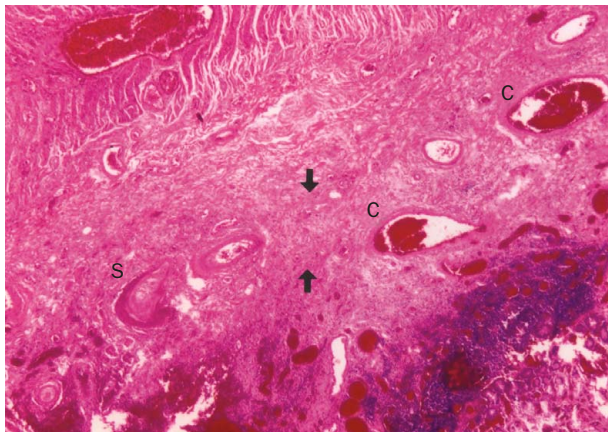
Figure 7. Watershed at ileocecal valve showing almost no transitional zone between the sclerotic vein (S, left) and 2 congested but non-sclerotic veins (C) in the proximal part (ileal mucosa at right lower corner; arrows: the supposed cut line of the watershed) (H&E, 50×).

calcification. The damaged veins usually have reactive myointimal hyperplasia, repeat the same mummified injury and calcification in it, and develop gradual occlusion of the lumens. Because in all cases with IMP (including ours), the more proximal colon is more affected and rectum is not or only mildly involved in severe cases, it could be considered that the ascending colon was affected first, and the lesion progressed to the distal side. However, what caused the injury?

For the etiology of IMP, several disorders such as diabetes mellitus, liver cirrhosis, postoperative change, exposure to toxic agents and aging process were speculated in past cases. However, common underlying or associated disease/condition of IMP has not been found. Chronic glomerulonephritis (in 1 of our patients) is not a common disorder either, and only Case 1 had laboratory evidence of liver disease. Phlebosclerosis has been reported to occur rarely in the portal vein and its branches caused by intrahepatic or extrahepatic portal obstruction, but without concomitant mesenteric phlebosclerosis,[11] and almost always occurs in patients with liver cirrhosis and portal hypertension. Calcification usually only develops in the late stage of such phlebosclerosis. In fact, hemodynamic change does not lead to mummified necrosis of venous wall in the early phase as seen in our case, and the absence of venous change in the appendix, which could not have the same venous return as the right colon, also indicates that this physical mechanism cannot be the cause of IMP. The remote abdominal blunt injury in 2 of our patients, even if there was occult localized hemodynamic change, would not be thought to cause such a widespread venous change in the colons as IMP (these 2 patients took herbs since the injury). Our cases

also lacked necrotizing vasculitis and mural thrombi as those shown under experimental injury of portal veins (such as administration of rolipram) with subsequent portal sclerosis similar to that of idiopathic portal hypertension.[12,13]

In 1999, Kitamura et al described a 56-year-old woman with some typical characteristics of CREST syndrome and getting phlebosclerosis in the ascending to transverse colon with the same histopathologic pictures as those demonstrated before.[14] There was also a striking fibrous replacement of colic muscle layer compatible with systemic sclerosis, and positive anti-centromere antibody and Raynaud's phenomenon were mentioned. They therefore speculated that the pathogenesis of the phlebosclerosis of the colon was related to CREST syndrome. However, all our cases lacked the clinical features of CREST syndrome, and anti-centromere antibody was not found in them or any of the other reported cases. It is unknown whether the anti-centromere antibody played the sole role or if there was another concomitant factor in the etiology of Kitamura et al's case, but the partial mummification of the media of the arteries in contrast to circumferential involvement of venous muscular wall in our cases seems to argue against this pathogenesis/etiology.

Losanoff et al commented on Iwashita's report and proposed a natural aging or various pathologic processes for the etiology of IMP. The great similarity of findings in our cases to Iwashita et al's, including the predominantly involved site, younger age of our patients, absence of appendiceal involvement and the presence of the same mummification in tissues other than venous wall, encourage us to speculate a cause rather than an aging process. The presence of our Taiwanese cases reduces the possibility of genetic susceptibility considered in the past due to only endemic cases in Japan.

Finally, Iwashita et al claimed that the social and occupational histories and clinical laboratory data of the patients offered no clues as to the cause. We think that environmental and dietary/toxic factors seem not to be readily ruled out in such a heavily polluted environment and only via crude survey of the ingested materials. In our patients, the common mummification and its unique zonal pattern of involvement in some tissues other than veins, together with the absence of venous lesion in the appendix that plays no obvious function in absorption, may hint that a toxic mechanism is still a possible cause of IMP. If so, certain toxins or biochemicals, which probably exist in the ingested contents and begin to be absorbed to the venous return at the terminal ileum or cecum, may predominantly damage the smooth muscle cells/reparative

myofibroblasts in veins and, after long-term deposition and perfusion, also damage the smooth muscle cells in the neighboring structures.

In conclusion, for at least a subgroup of cases of IMP and based on the previously unrecognized findings, we suggest that IMP is initiated by a slow but longstanding and direct hypoxic injury to the venous muscular layer, which leads to gradual mummification and then sclerosis and calcification in this layer. The change is followed by the repeated same damage of the subsequent reactively hyperplastic myointima in the veins, and they finally result in gradual venous occlusion. In this group, certain toxins or biochemicals probably existing in the frequently ingested contents and absorbed to the venous return may play the most important role in the damage. However, analysis of more cases is required to support the proposal, and if such support is found, the toxic agents still remain to be clarified via further investigations.

Acknowledgments

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