Idiopathic Mesenteric Phlebosclerotic Colitis: A Case Report

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Idiopathic mesenteric phlebosclerosis (IMP) is a rare cause of chronic intestinal ischemia. Its clinical manifestations include chronic abdominal pain and/or chronic diarrhea, which are nonspecific and often lead to a delayed diagnosis. IMP is diagnosed based on characteristic radiographic findings of threadlike calcifications in the mesenteric veins coupled with unique pathologic findings. The cause of the disease and pathogenesis remain unknown. Herein, we present a 46-year-old woman who was hospitalized with complaints of chronic abdominal pain and diarrhea for 10 years and a loss of 20 kg in body weight. Colonoscopy revealed diffuse ulcerations and treatment for inflammatory bowel disease was administered. Two weeks after discharge, she returned to our emergency department because of acute abdominal pain. Plain abdominal radiography and computed tomography revealed calcifications and stenosis of the mesenteric veins and accumulation of free air, indicating possible colonic perforation. Emergency surgical intervention and a subtotal colectomy and ileostomy were performed. Pathologic findings confirmed the diagnosis of mesenteric phlebosclerotic colitis. Her postoperative course was complicated by sepsis and she died on postoperative day 3. We hope that this report serves to alert physicians of this potentially life-threatening disease.

Key words: idiopathic mesenteric phlebosclerosis, mesenteric phlebosclerotic colitis, chronic diarrhea, chronic abdominal pain

Introduction

Mesenteric atherosclerosis is a common cause of chronic intestinal ischemia(1), while mesenteric phlebosclerosis is a rarer and less understood cause(2). Iwashita et al. reported the first case of mesenteric phlebosclerosis in 1989(3,4), and subsequently reported seven similar cases in 2003(5). The authors suggested that this disorder, called idiopathic mesenteric phlebosclerosis (IMP), should be considered a new disease entity with an unknown cause and pathogenesis.

IMP is characterized by non-thrombotic, non-obstructive sclerosis of the mesenteric veins that leads to enteric ischemia. The seven cases reported by Iwashita et al. all demonstrated non-specific clinical symptoms such as abdominal pain and diarrhea which were of slow onset and progression. Stool occult blood was detected in four of the seven cases, and mild anemia was found in five. Plain abdominal radiographs revealed threadlike calcifications in all cases, and barium enema images showed right-side colonic stenosis. Colonoscopy further revealed edematous mucosa that appeared...
dark red with multiple ulcers. Because of persistent abdominal pain and bowel obstruction, five patients received partial colectomies (four subtotal colectomies and one right-sided colectomy). Examination of the surgical specimens revealed the colonic surface to be dark purple to dark brown and the plicae semilunares coli were edematous or absent. Microscopic findings included prominent fibrosis, thickened and calcified venous walls, fibrosis and collagen accumulation in the submucosa, and foamy macrophages in the vascular walls.

Delayed diagnosis of IMP is common because of the rarity of the disease, non-specific clinical symptoms, and slow but persistent progression. We herein present the case of a 46-year-old woman with IMP. It is our hope that this report may serve as a reminder for clinicians of the diagnosis and management of this rare condition.

**Case Report**

A 46-year-old woman was seen at our hospital with complaints of chronic abdominal pain, diarrhea, and bloody stool. In recent years, she had experienced many episodes of abdominal pain and diarrhea, had been seen frequently in the outpatient departments and emergency departments of local institutions, and had been hospitalized several times. She had been treated for conditions such as infectious diarrhea, peptic ulcer disease, and irritable bowel syndrome, and had a 20 kg weight loss in the past 10 years. Over the past 12 months, she had been admitted several times for chronic diarrhea, abdominal pain, anemia, and sometimes fever. Over the course of the admissions, the symptoms subsided with the administration of antibiotic therapy, and she was reluctant to receive further diagnostic testing such as colonoscopy and radiographic imaging studies. Several months prior to admission in our ward, she was hospitalized for several weeks and treated for a liver abscess at a medical center. Her past history was significant for iron deficiency anemia of unknown origin and she was a hepatitis B virus carrier. She denied tobacco or alcohol consumption and was employed as a public service worker. She described consuming “invigorant water” (of unknown content) as a detoxification treatment suggested by a folk medicine practitioner for over 10 years. Physical examination revealed the patient to be emaciated (height, 162 cm; body weight, 38 kg) with a body temperature of 37.8°C. No specific point tenderness of the abdomen was noted, but mild ascites was present. Laboratory tests revealed a hemoglobin concentration of 7.9 g/dL, white blood cell count, 9100/mL, serum glutamic-pyruvic transaminase, <5 U/L; alkaline-phosphatase, 91 U/L (normal, 60-240 U/L); albumin 1.7 g/dL; and potassium, 3.2 mEq/L, suggesting severe malnutrition. Testing for heavy metals revealed a blood lead concentration of 8.2 μg/dL; cadmium, 1 μg/L; and copper, 925 ppb, all within the normal ranges. Routine urine tests were normal. Stool specimens were found to contain neutrophils and *Aeromonas* species, but no ova or parasites were present. Laboratory analysis of the ascitic fluid showed no signs of infection, and bacterial cultures showed no growth. A polymerase chain reaction assay done on the ascetic fluid for *Mycobacterium* was negative.

Because of severe malnutrition, anemia, and bowel symptoms, further diagnostic testing was done. An upper gastrointestinal endoscopy revealed esophageal candidiasis, and a small bowel series revealed irregular mucosal surfaces on the terminal ileum and the ascending colon, corresponding to inflammatory bowel disease (IBD) (Fig. 1). Colonoscopy revealed swollen and injected colonic mucosa, and diffuse ulcers and multiple nodular lesions were seen in the ascending and sigmoid colon (Fig. 2). Biopsy revealed significant inflammation and ulceration consistent with IBD.
Fig. 1  Small bowel series. An irregular colonic lumen surface, indicating chronic inflammation, is revealed by barium flowing into the ascending colon

Fig. 2  Colonoscopy. Multiple nodular lesions, 5-8 mm, are seen scattered throughout the entire colon except for the rectum. There are numerous ulcers of varying sizes (1-3 cm) between the nodules. The ulcers are filled with white material at the center and ringed with red, swollen tissue
Under the impression of IBD, oral mesalazine (800 mg bid) and prednisolone (10 mg qid) were administered and she was discharged from our hospital.

Two weeks later the patient returned to the emergency department with acute abdominal pain. Physical examination revealed signs of peritonitis and a plain abdominal radiograph revealed free air and threadlike calcifications in the right lower quadrant in a pattern that resembled that of the mesenteric veins (Fig. 3). Abdominal computed tomography (CT) revealed stenosis and calcification of the superior mesenteric vein, inflammation and thickening of the colic wall, ascites, and free air in the abdomen (Fig. 4). The working diagnosis was colic ulcer complicated by perforation, and emergency surgery was performed. Intraoperatively, almost the full length of the colon except for the rectum was found to be ischemic; therefore, a subtotal colectomy and ileostomy were performed. The patient developed sepsis postoperatively and she died on postoperative day 3.

Grossly, the surgical specimen was dark red with edematous mucosa, and the plicae semilunares coli were absent in several regions. While multiple ulcers (ranging from 0.3 cm to 2.0 cm) were seen throughout the colon, lesions along with deep fissures were more concentrated in the proximal colon. Several ulcers were also found in the terminal ileum, but there were not as many and they were not as deep as in the proximal colon. No obvious perforation was visible, but suppurative exudates covering some areas of the serosa and omentum were noted, indicating microperforations. The colonic wall in non-ulcerated regions was prominently thickened and calcified vessels were easily palpable. Microscopic examination revealed fibrosis, thickening, and sclerosis of the venous walls, as well as scattered calcifications (Fig. 5). The venous lumens were strikingly narrowed or completely occluded. Few inflammatory cells were present in the vascular wall. Collagen accumulation in the mucosa, significant submucosal fibrosis, and thickening of the colonic wall were also noted (Fig. 6). No significant pathological findings were
Fig. 4 Abdominal computed tomography showing calcified mesenteric veins in the right lower quadrant. The image is a cross-section through the mesenteric veins. Massive free air is shown at the top of the image.

Fig. 5 Microscopic examination reveals mesenteric phlebosclerosis. On the left is a cross-section of a vein with thickening and calcifications. By contrast, no calcifications are noted in the artery (right).
Fig. 6 Microscopic examination showing multiple ulcerations and prominent thickening of the colonic wall in the non-ulcerated areas. The left half of the image is an area where the colonic wall is thickened. Significant accumulation of collagen in the mucosa and fibrosis in the submucosa are noted. An ulcer is clearly visible to the right of center.

revealed in the mesenteric arteries except for a mildly thickened tunica intima and media, which could have been secondary to increased peripheral resistance.

The conclusion drawn from the above findings suggested a long-term pathological process that led to the venous changes. The process was considered to be a state of ischemia caused by chronic congestion, stasis, and decreased venous return which progressed to mucosal bleeding, erosion, and ulceration, and as collagen accumulated in the mucosa, significant submucosal fibrosis and thickening of the colonic wall developed. The above characteristic pathological manifestations confirmed the diagnosis of IMP complicated by ischemic changes, multiple ulcerations, and microperforations.

**Discussion**

While most instances of vascular occlusion-related ischemic diseases of the bowel are caused by embolism or clots in the mesenteric arteries, cases which are the result of obstructed mesenteric veins are less common. Most cases of mesenteric vein occlusion are the result of thromboembolism. Non-embolic causes of mesenteric vein obstruction or stenosis are extremely rare and include CREST syndrome \(^6\), Churg-Strauss syndrome (allergic granulomatous angiitis syndrome) \(^7\), venulitis associated with systemic lupus erythematosus, Behcet’s disease \(^8\), enterocolic lymphocytic phlebitis \(^9\), idiopathic myointimal hyperplasia of the mesenteric veins, and mesenteric inflammatory veno-occlusive disease \(^10\)\(^-\)\(^12\). In 1989, Iwashita et al. proposed mesenteric phlebosclerosis as a novel pathological mechanism of mesenteric vein obstruction \(^3\). Later, in their 2003 study the same authors reviewed the clinical and pathological data drawn from seven cases at their institution and fourteen other cases in the literature \(^5\). They
identified that fibrosis, thickening, and sclerosis of the venous walls are the unique pathological findings of mesenteric phlebosclerosis compared with the other abovementioned causes of venous obstruction\(^5\). Additionally, as Iwashita et al. failed to identify the characteristic clinical symptoms of other uncommon causes of mesentery ischemia, such as Degos symptoms, Wegener’s granulomatosis, and polyarteritis nodosa, they concluded that mesenteric phlebosclerosis is a different disease entity\(^10\). Consequently, Iwashita et al. named the condition idiopathic mesenteric phlebosclerosis. The patient described in the present report was also affected with IMP.

Although studies following those of Iwashita have continued to adopt the terminology of IMP, neither the originator nor the adherents of the term have determined whether it is a primary disorder, a chronic pathological result of other diseases, or a consequence of long-term medical treatment for other diseases. If its true origins are to be explored, the fact that most IMP cases have occurred in individuals of Japanese ethnicity must be considered. Fifteen cases reported by Koyama et al. in 1991 were all in Japanese individuals\(^13\). Among the 24 cases reviewed by Kimura et al. in 2003, there were 23 Japanese patients and one Taiwanese\(^14\). In 2005, another case of IMP believed to be the first in the Americas was reported in the United States; of note, the patient was a Taiwanese immigrant\(^15\). Therefore, IMP can be assumed to be related to race through potential genetic mechanisms, dietary habits, or long-term medication use. Coincidentally, both our patient and her husband had consumed folk medicine water for a long time. One month after the death of our patient, the husband complained of the same symptoms. His abdominal radiograph revealed calcifications in the right lower quadrant, and the results of a colonic biopsy were consistent with mesenteric phlebosclerotic colitis.

In 2009, Miyazaki et al.\(^16\) reported a married couple who both had IMP colitis. Racial or genetic explanations for the husband and wife to contract such an infrequently seen disease seemed less possible than dietary, medicinal, or environmental factors. Drug-induced phlebitis has been reported. Larson et al.\(^17\) showed that rolipram (a selective inhibitor of type IV phosphodiesterase isoenzymes) induced vascular inflammation and necrosis in the mesenteric and portal arteries and veins in a murine model. A 1989 study indicated that rutoside, a medicine for treating varicose veins in Europe, was associated with bowel ischemic necrosis\(^18\). In 1992, a case report by Ohashi et al. also suggested that some water-soluble irritants might precipitate chronic ischemic colitis by triggering calcification in the colic veins\(^19\). When Iwashita et al. proposed mechanisms for IMP, drug-related factors were excluded because of a lack of history of long-term drug use among their subjects and the absence of inflammatory cells, especially eosinophils, in the vascular walls, which would be a pathological indication of a drug effect\(^5\). However, since the number of inflammatory cells decreases, and fibrosis and calcification increase as a chronic disease progresses into later stages, we suggest that the potential role of drugs in the onset of IMP cannot be ruled out.

To explore whether certain factors predispose a person to IMP, previous studies were reviewed. No common history of illnesses was found among the patients reported, although some cases of pre-existing diabetes, hyperlipidemia, and liver cirrhosis were noted. Since the patient age range is from 36 to 77 years, age does not appear to be a direct factor. Some patients with IMP experienced mild symptoms for as long as 3.5 years and only observation was required, while in another patient only 2 months transpired from disease onset to right-side colectomy\(^5\). Thus, it appears that the length of symptoms is not necessarily related
to disease severity, or at least it is not the only determinant. Although no particular cause or risk factor has been confirmed, we believe that IMP has a unique pathological process (5,14,20). For example, the varying onset of the disease is distinct from other common causes of ischemic colitis. Other features of IMP which differ from known ischemic bowel diseases are as follows: (1) In all cases, the right side of the colon is involved, while in some cases the lesion extends to the distal colon; (2) Calcification in the mesenteric veins can be identified by abdominal X-ray radiology or CT; (3) Colonic stenosis or thumbprinting can be identified by barium enema images; (4) Dark purple and edematous mucosa accompanied by ulcers and a narrowed lumen can be identified on colonoscopy; and (5) Submucosal fibrosis around blood vessels and thickened venous walls with fibrosis, hyalinization, and calcification are seen on microscopic examination.

Since the clinical symptoms of IMP, including abdominal pain, diarrhea, constipation, and bowel obstruction, are nonspecific, patients with IMP are often mistakenly treated for common gastrointestinal diseases, and thus the diagnosis is delayed. The patient in this report visited outpatient clinics and emergency departments numerous times, and had several hospitalizations, but was never diagnosed with IMP. For that reason, the combination of a detailed history, radiographic workup, and pathological examination is required to confirm the diagnosis. One of the major characteristics of IMP is calcifications identified on plain abdominal radiographs, but this can also be found in patients with colon cancer, chronic colonic infections, and atherosclerosis (21). However, close inspection reveals the calcification pattern of IMP which centers in the right lower quadrant in a threadlike pattern, distinct from that of other diseases. While evidence of bowel stenosis on barium enema examination can also be found in other chronic inflammatory bowel diseases, the findings of IMP, including narrowing of the lumen and thumbprinting, are markedly right-sided.

Gross examination and histopathological studies can help differentiate IMP from other inflammatory bowel diseases based on its unique findings. Nevertheless, without a history or radiographic diagnosis, sole reliance on colonoscopy biopsy might still lead to wrong conclusions because of sampling errors, such as obtaining specimens from a less affected site, non-specific ulcerated regions, or from congested mucosa, or mistaking calcified veins for arteries when only a hematoxylin and eosin stain is performed. Some studies report that colonoscopic sonography findings, such as a thickened colic wall and calcified vessels in the right-side of the colon, can serve as auxiliary evidence in some cases (20).

Treatment strategies for IMP are surgery-based, but the timing of intervention has yet to be determined. In the report of Iwashita et al., five of seven patients received surgery, but the timing and reasoning were not discussed. The other two patients who underwent conservative treatment (5), had histories of IMP for 7 months and 3.5 years, and had been followed-up for 9 years at the time of publication. Of note, barium enema prior to surgery showed an apple-core lesion in one of the patients, and pathological study later confirmed colon cancer. Another study has also reported a case in which examination of the surgical specimen revealed not only mesenteric phlebosclerotic colitis but also colon cancer (14). Further case analysis is needed to conclude whether mesenteric phlebosclerotic colitis acts as a risk factor for colon cancer. Although chronic symptoms including abdominal pain and diarrhea were physically endurable in our patient, complications such as perforation coupled with pre-existing malnutrition led to her death, despite surgical intervention. Therefore, nutrition supplementation after diagnosis and early surgical
intervention to prevent possible complications should be considered.

To date, the only case reports of IMP have originated from Japan and Taiwan and suggest that the condition is likely due to genetic or dietary factors or long-term use of certain drugs. Further exploration of all possible causes requires an epidemiological perspective on geographic proximity, familial screening, and a more detailed history and analysis that include an inquiry into the use of folk remedies. We believe that the cause of IMP will become elucidated with an increasing number of case reports being published.

References

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不明原因腸系膜靜脈硬化性大腸炎：一病例報告

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不明原因腸系膜靜脈硬化是引起慢性腸道缺血的一個罕見原因。在臨床上，主要是以慢性腹痛或腹瀉表現，但因其為非特異症狀，所以診斷上常會延誤。確定診斷主要是靠放射線檢查看到腸系膜靜脈線狀鈣化，加上病理學上特殊的表現來加以診斷。但其確切的病因及致病機轉，目前並無定論。本文報告一名46歲女性，有慢性腹痛及腹瀉症狀已達10年，並有體重減輕約20公斤。住院時大腸內視鏡檢查發現瀰漫性大腸潰瘍，初步診斷為發炎性大腸疾病，於門診追蹤治療；但出院兩週後因急性腹痛至急診，接受腹部X光及腹部電腦斷層檢查時，始發現有腸系膜靜脈鈣化及狹窄，並有游離空氣，懷疑有腸穿孔。病患接受緊急手術，病理檢查診斷為不明原因腸系膜靜脈硬化性大腸炎。此病患終因重度營養不良，術後併發敗血症而死亡。期望藉由本病例報告，讓臨床醫師對此潛在致命的疾病多加了解。

關鍵詞：不明原因腸系膜靜脈硬化症，腸系膜靜脈硬化性大腸炎，慢性腹瀉，慢性腹痛