Idiopathic Myointimal Hyperplasia of Mesenteric Veins

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Nonthrombotic occlusion or stenosis of the mesenteric veins is a rare cause of intestinal ischemia that usually occurs in association with systemic vasculitis. The current report includes four male patients with segmental ischemic colitis caused by idiopathic myointimal hyperplasia in the small mesenteric veins and their intramural branches; neither vasculitis nor arterial involvement were present. Three of the four patients were ≤38 years of age; the fourth was 67. All four patients were previously healthy and had no history of drug use of any kind. Clinical findings included abdominal pain, diarrhea, bloody stools, and colonic strictures discovered by barium enema. The intima of the mesenteric and intestinal mural veins was focally thickened by a marked increase in cells and matrix between the endothelium and internal elastic lamina, whereas the vessel walls external to the thickened intima appeared normal. Histochemistry and immunoreactivity with antibodies to muscle-specific actins (HHF-35) disclosed that the intimal thickening was caused by proliferation of smooth muscle cells in a proteoglycan matrix. All patients recovered completely after segmental resection of the ischemic portion of the colon and had no recurrence of intestinal symptoms on follow-up of up to 7 years. These unusual venous lesions do not appear to have been previously described; their etiology and pathogenesis remain unknown.

Intestinal ischemia may be caused by stenosis or occlusion of the mesenteric arteries or veins or by decreased vascular perfusion without vascular lesions. Most cases of occlusive mesenteric ischemia are secondary to arterial thromboembolism (1). Venous occlusion is an uncommon cause of ischemic bowel disease and is usually caused by thrombosis that may occur as a complication of a wide variety of conditions (2). Rare nonthrombotic causes of mesenteric venous occlusion include venulitis associated with systemic lupus erythematosus (3), Behçet's disease (4), and a recently described enterocolic lymphocytic phlebitis that may be associated with the use of rutoside, a drug used in Europe for the treatment of varicose veins (5). We report cases of four patients with idiopathic myointimal hyperplasia of the mesenteric veins, a cause of ischemic colitis that does not appear to have been recognized previously.

Materials and Methods

Resected segments of colon from four male patients were studied, all of which had been referred to one of the authors (R.C.H.) for a consultative opinion. In each case, the clinical history was reviewed and follow-up information was obtained from the attending physician. Each patient had undergone a segmental colectomy, and the resected segment of colon was available for histological examination. Multiple 5-μm sections from the colon and adjacent vessels were stained with H&E, Masson trichrome, Verhoeff-van Gieson elastic stain, and Movat pentachrome stain. Sections from two cases were reacted with the following antisera: HHF-35, diluted 1:8000 with 5 mmol ethylenediamine tetraacetic acid (EDTA) (Enzo Biochemical, New York, NY), for the evaluation of muscle-specific actins; factor VIII-related antigen, diluted 1:250 and with 10-minute pronase digestion (Dako Corporation, Santa Barbara, CA), for endothelial antigens, and HAM-56, diluted 1:4000 (Enzo Biochemical), for the evaluation of macrophage antigens. The antibodies were localized via the avidin-biotin immunoperoxidase technique.

Sixty consecutive, unselected colectomy specimens from patients who had undergone resection for colonic adenocarcinoma were evaluated for mesenteric vascular lesions as a normal control group.

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Case Reports

Case 1

A 30-year-old white male naval aviator presented in September, 1982, with a 1-month history of lower abdominal pain associated with bright red blood in his stools. The patient had been in excellent health and was taking no medications. Barium enema revealed a stricture in the sigmoid colon, and an elective sigmoid resection was scheduled. However, 1 week before the scheduled surgery, a complete bowel obstruction developed and the patient underwent an emergency resection of the sigmoid colon.

The specimen consisted of a segment of colon measuring 22 cm in length and up to 8 cm in diameter. A 5.0-cm patch of firm, yellowish white exudate adhered to the serosa and corresponded to a mural thickening that reduced the colonic lumen to a diameter of 1.5 cm. A deep ulcer 6 cm in diameter and apparently extending through the bowel wall was present within the stricture.

The patient has had no further abdominal complaints and 7 years after his colonic resection is on active duty and free of symptoms.

Case 2

A 38-year-old white male physician presented in September, 1990, with a 2-month history of cramping abdominal pain and diarrhea alternating with constipation, mucoid, blood tinged stools, and, finally, hematochezia. Flexible sigmoidoscopy showed an actively bleeding rectal ulcer and mild colitis in the left colon. Abdominal radiographs, ultrasound, and computed tomography scans were unremarkable. The patient was stabilized and treated with topical steroids and antispasmodic agents. Plans for colonoscopy to evaluate the clinical impression of inflammatory bowel disease were made, but progressive pain, obstipation, and proctalgia developed and the patient continued to have mucoid, blood tinged stools. A repeat flexible sigmoidoscopy showed marked erythema and edema with superficial ulcerations in the sigmoid and descending colon; biopsy specimens were said to be consistent with ulcerative colitis. Because of progressive deterioration in the patient's status and the development of an incipient toxic dilatation of the colon, he underwent an abdominal colectomy with ileostomy and Hartmann pouch.

The colectomy specimen consisted of a 98-cm segment of colon, the distal 28 cm of which was markedly thickened. The mesenteric fat was indurated. The mucosal surface was necrotic and hemorrhagic, and the muscular wall was thickened to 1.4 cm. At the proximal limit of the thickened segment, polypoid excrescences of mucosa measured up to 2.3 cm in diameter. The patient had an uneventful postoperative recovery and underwent an ileorectal anastomosis in January 1991.

Case 3

A 25-year-old white tackle shop salesman and fishing guide, with no history of previous health problems or medications, developed progressive abdominal pain, alternating constipation and diarrhea, and rectal bleeding over a period of several months in the fall of 1984. A tentative diagnosis of ulcerative colitis was made, but colonic biopsies obtained in December 1984 and in January and February 1985 were interpreted as essentially normal. An additional biopsy specimen from the sigmoid colon at 25 cm, obtained in February 1985, was reported as showing acute necrotizing inflammation. In March 1985, the patient developed an acute abdomen and underwent an exploratory laparotomy during which a 20 cm segment of rectosigmoid colon was resected and a Hartmann pouch was constructed.

The resected specimen consisted of an edematous, hemorrhagic, and focally necrotic segment of large bowel with extensive deposits of fibrinopurulent exudate on the serosal surface. The mucosa was hemorrhagic, necrotic, and covered with yellow purulent material. The mesocolon was congested and focally indurated.

A complete recovery followed the procedure, and follow-up rectal biopsy specimens taken in August 1985, were interpreted as showing moderate inflammation. In October 1985, the colostomy site was closed, and the patient returned to excellent health. He has been followed up at regular intervals since 1985 and was free of symptoms in March 1989.

Case 4

A previously healthy 67-year-old white male salesman developed lower abdominal pain, cramps, constipation, and diarrhea (up to 15–20 bowel movements a day) in April 1987, while traveling away from home. His past medical history was unremarkable, and he was taking no medications. A tentative diagnosis of Crohn's disease was made, and the patient was given sulfasalazine without substantial improvement. In June 1987, barium enema showed a 6 cm narrowing in the sigmoid colon; colonoscopy revealed changes consistent with ischemic colitis in the area of the sigmoid, and multiple biopsy specimens obtained at that time were interpreted as being consistent with ischemic colitis. An abdominal angiogram was interpreted as normal. Repeat colonoscopies showed ulcers in the rectum and patchy colitis. The patient's condition became progressively worse with severe lower abdominal pain and many loose stools per day that were frequently streaked with blood. In July 1987, a sigmoid resection and construction of a Hartmann pouch was performed.

The resected segment of colon measured 28 cm and showed marked thickening of the submucosa. Erythematous areas and innumerable depressed granular lesions in the mucosa extended throughout the length of the specimen. The mesocolic fat was fibrotic and focally necrotic.

The patient was discharged from the hospital fully recovered, and no further interventions were deemed necessary on follow-up visits. In January 1989, he was reported to be in excellent health.

Histological Findings

The resected segments of colon showed varying degrees of ischemic injury that varied in extent
and severity in different patients. The ischemic lesions ranged from superficial mucosal necrosis with regenerative epithelial hyperplasia (Figure 1) to transmural necrosis. Vascular congestion and extravasation of red blood cells affected all layers of the bowel wall. Hemosiderin-containing macrophages were scattered in the submucosa and muscularis propria and were present in greatest numbers in the serosa. Focal fibrosis of the lamina propria, muscularis mucosae, and muscularis propria was present in all cases, as were ulcers with bases composed of granulation tissue. These histological changes produced an appearance that was indistinguishable from ischemic colitis caused by arterial stenosis; however, no significant arterial lesions were identified.

The distinctive feature in each case was striking intimal thickening involving small mesenteric veins and their intramural branches (Figures 2–4). The intimal thickening was usually circumferential but occasionally eccentric. Affected veins were located only in the abnormal segments, where they were found in the mesentery, muscularis propria, and submucosa, and ranged from 0.15 to 1.0 mm in diameter. In some cases the intimal thickening resulted in complete or near complete occlusion of the vascular lumen (Figures 2 and 3). The cells responsible for the intimal thickening were spindle shaped with eosinophilic cytoplasm and elongated oval nuclei with bluntly rounded ends (Figure 4). The intimal cells were embedded in a matrix of granular alcian blue–positive material. External to the thickened intimal region, essentially normal venous wall was present except for focal slight neovascularization of the media and adventitia (Figure 4). The intimal cells reacted strongly with monoclonal antibody HHF-35 to muscle-specific actins (Figure 5), whereas neither factor VIII–related antigen nor macrophage antigens were detectable. These findings indicate that the intimal thickening was caused by proliferation of smooth muscle cells in a proteoglycan matrix.

A modest degree of eccentric intimal thickening was also present in some of the arteries, but this was not a constant finding. In fact, Verhoeff–van Gieson elastic stains revealed that in most cases the markedly

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Figure 1. Case 1. The colonic mucosa is affected by ischemic necrosis with regenerative epithelial hyperplasia and minimal inflammation (H&E; original magnification ×100).

Figure 2. Case 3.
A. A small mesenteric vein measuring 0.4 mm in diameter can be seen in the mesenteric adipose tissue and extending through the muscularis propria to the submucosa at the top of the photograph. The artery to the left of the vein appears histologically unremarkable (H&E; original magnification ×25).
B. At higher magnification, the thickening of the venous wall can be seen to be due to proliferation of cells between the endothelium and media. Note the normal arterial wall (H&E; original magnification ×50).
thickened veins were accompanied by essentially normal arteries (Figure 3). Arterial thrombi, emboli, or features suggestive of atherosclerotic vascular disease could not be shown in any sections, despite careful searching.

In none of the cases was there evidence of primary vasculitis affecting either arteries or veins. Localized necrotizing vasculitis and fibrin thrombi were seen beneath and adjacent to ischemic ulcers and necrotic areas; however, we disregarded these changes because they are consistently present as a secondary phenomenon around nonspecific ulcers and necrotic lesions that are unrelated to ischemia (6).

Eight of the 60 normal control specimens had atherosclerotic thickening of some branches of the mesenteric arteries, but none had venous lesions resembling the myointimal hyperplasia seen in the four cases. The absence of venous lesions in 60 control specimens provides a 95% confidence level that such lesions would not be found were a larger control sample to be studied (7). The ages of the control group (mean, 65; median, 62 years) were higher than those of the four cases (24, 25, 38, and 67 years); however, if anything, one would anticipate a higher prevalence of venous lesions in the older control group. Accordingly, we do not think that the older age of the controls represents a confounding bias and conclude that myointimal hyperplasia of mesenteric veins is not seen in the normal population.

Discussion

Nonthrombotic occlusion of the mesenteric veins has previously been reported as a cause of intestinal ischemia in a small number of cases; however, none of them appears to represent the condition reported here. Modigliani et al. described a patient with prominent intestinal symptoms caused by allergic granulomatous angiitis (the Churg–Strauss syndrome) involving the mesenteric veins (8). Behçet’s disease (4) and lymphocytic phlebitis (5) have been reported to cause mesenteric ischemia by selectively affecting the veins. Mesenteric venulitis may accompany the predominantly arterial vasculitides of lupus erythematosus (3), rheumatoid arthritis (9,10), and Buerger’s disease (11). However, in none of these conditions are the veins narrowed or occluded by a noninflammatory myointimal proliferation such as that seen in these patients. The histological appearance of the lesions and the lack of cutaneous and systemic manifestations exclude rare causes of mesenteric ischemia such as the Degos’ syndrome (12), Wegener’s granulomatosis (13), polyarteritis nodosa (14), and other primary vasculitides (15). Similarly, drug-related vasculitis can be excluded because of the lack of arterial and arteriolar involvement, the absence of inflammatory cells, particularly eosinophils, complete sparing of the skin, and absence of a history of drug ingestion (16). Venous lesions similar to those reported here were noted by Schwartz et al. in patients who had taken a combination of hydrochlorothiazide and enteric-coated potassium chloride (17). In the resected ileum, intimal edema and proliferation in the mesenteric arteries and partially obliterative endophlebitis in the accompanying veins had caused ischemic ulcers and strictures (17). The venous lesions illustrated by these authors bear a striking resemblance to those we have observed; however, none of our patients was hypertensive and none was taking diuretics or potassium supplements. Thus, we can exclude this etiology in our cases. Idiopathic intimal hyperplasia has been reported to occur in small mesenteric arteries and arterioles (16–20), but venous involvement was not mentioned in these reports. A venous lesion similar in some respects to that seen in these patients has been described in saphenous veins used for aortocoronary bypass grafts.
Figure 4. Case 4.

A and B. This mesenteric vein measured 0.5 mm in diameter. Note the proliferation of spindle cells with oval nuclei in the intimal region. The elastic lamina (black) demarcates the thickened intima from the media. There is slight neovascularization of the media (Movat pentachrome stain; original magnification \( A \times 100, B \times 180 \)).

Figure 5. Case 4. Localization of antibody HHF-35, directed against muscle-specific actins, discloses that the cells in the thickened intima are smooth muscle cells. The nonstaining elastic lamina separates the thickened intima from the media (arrow) (original magnification \( \times 180 \)).

and has been variously attributed to perfusion of the vein under high pressure (21) or to be immunity mediated (22). With regards to increased high pressure venous perfusion as a cause of myointimal hyperplasia, we have seen ischemic colitis secondary to this lesion in the resected colon of a 24-year-old man who had angiographic and histological evidence of an arteriovenous fistula with increased venous flow confirmed by angiography. We have also seen myointimal hyperplasia of mesenteric veins produce an ischemic stricture in the residual colon of a 58-year-old woman who underwent a left hemicolectomy for adenocarcinoma 3 years earlier. This patient was not included in this series because of the previous surgical manipulation of the affected colon. Because arteriovenous fistulas have been reported to follow intestinal resection (23), one could speculate that this patient developed an arteriovenous fistula, increased venous blood flow, myointimal hyperplasia of the mesenteric veins, and an ischemic stricture as the ultimate consequence. None of the four cases presented here had any clinical or pathological evidence of an arteriovenous fistula as a possible explanation for their myointimal hyperplasia; however, none of them had an arteriogram to look for such evidence. The occupational and social histories of these patients offer no clues as to the etiology of the mesenteric vascular lesions.

The fact that the sigmoid colon was affected in all four patients (along with the descending colon in two and proximal rectum in two) suggests that this condition might preferentially involve the vessels of the left
colitis, i.e., in the distribution of the inferior mesenteric vasculature. Study of additional cases will be required to confirm this prediction.

Because it is believed to be uncommon, a venous source of intestinal ischemia is rarely suspected. Angiographic evidence of venous narrowing or occlusion may be overlooked unless it is considered and sought by careful examination (24). Endoscopic biopsies of the colon may show the characteristic mucosal changes of ischemic colitis (25) but do not differentiate an arterial from a venous cause. Thrombosis of mesenteric veins typically leads to gross edema and hemorrhagic infarction of the bowel, but as the lesion matures, it assumes an appearance that closely resembles the late effects of arterial occlusion (26). By the time histological material becomes available, determining whether the original cause of the lesion was arterial or venous might not be possible, although it has been proposed that an abundance of hemosiderin-laden macrophages suggests a venous rather than an arterial lesion (26). Only careful gross dissection and microscopic examination of the mesenteric vessels allows a determination of the precise location and nature of the vascular lesions. In some of the cases reported here, the veins were so prominent that many were larger and thicker than their accompanying arteries. A cursory examination of H&E-stained sections, without the use of elastic stains, could have easily led to the conclusion that the lesions were arterial.

Idiopathic inflammatory bowel disease was considered in the initial diagnostic assessment of three of our patients. All three were treated with corticosteroids or sulfasalazine, or both, until their deteriorating clinical condition, severe rectal bleeding, and development of an acute abdomen, respectively, provoked exploratory laparotomy and segmental colectomy. Venous lesions like those described here have not been reported in either ulcerative colitis or Crohn's disease. Although the initial delay in reaching the diagnosis could probably have been reduced in some of these patients if the possibility of ischemic colitis had been considered earlier, the nature of the lesions responsible for the ischemic injury could not have been predicted. These patients emphasize the point that intestinal ischemia is not limited to elderly patients with atherosclerotic cardiovascular disease. Nonocclusive Intestinal ischemia may occur in young people with no known associated diseases (27,28) and in some athletes after strenuous exercise (29,30). Unexplained mesenteric vein thrombosis has been documented in young women taking oral contraceptives or estrogens (27,31); however, it has also occurred in healthy young persons with no identifiable risk factors (32,33). Most of these cases apparently resolve spontaneously and do not recur.

In summary, these male patients with myointimal hyperplasia of the mesenteric veins developed ischemic colitis and segmental colonic strictures that required surgical resection. The gross and histological appearance of the lesions, apart from the thickened veins, was indistinguishable from that seen with chronic ischemic ulcers and strictures associated with vascular hypoperfusion in the absence of vaso-occlusive lesions and with arterial stenosis (9). The process is either self-limited or indolent, because none of the patients has had a recurrence of abdominal symptoms after follow-ups up to 7 years. None of the patients had previous or concomitant intestinal or vascular disease or other known medical conditions. None of them was taking either prescription or over-the-counter medications, none had unusual dietary habits or admitted use of illicit drugs, and none had an unusual occupational or social history. The occurrence of similar lesions in two patients known or suspected to have increased mesenteric venous perfusion caused by arteriovenous fistulas raises the question whether increased venous perfusion could have been present in these patients; we have no evidence showing that this was the case but cannot completely exclude it. Thus, based on the information available, the condition appears to be idiopathic and not previously described; determining whether it represents a single, specific entity will require the identification and investigation of additional cases.

References

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