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Alessandro Corsi · Sergio Ribaldi · Massimo Coletti
Cesare Bosman

Intramural mesenteric venulitis

A new cause of intestinal ischaemia

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Abstract Venous damage is an uncommon cause of intestinal ischaemia. We report on a 44-year-old woman who presented signs and symptoms of acute intestinal ischaemia requiring surgical treatment. Histological examination of the resected right colon showed features of an intramural lymphocytic venulitis with no other demonstrable causes of ischaemic injury of the bowel. Extramural mesenteric veins appeared dilated and congested, without evidence of thrombotic occlusion or of inflammatory involvement. The patient, who was not taking any long-term medication and had no clinical evidence of collagen-vascular disease, promptly recovered after surgery. Follow-up for 7 months with no recurrences suggested a self-limited or indolent process. We propose the name 'intramural mesenteric venulitis' for this condition and believe that it could represent one extreme (the microscopic variant or intramural phase) of the spectrum comprising entero-colic phlebitis and mesenteric inflammatory veno-occlusive disease. The immunohistochemical evidence of a marked preponderance of T phenotype in the perivenular lymphocytes suggests lymphocyte-mediated vascular damage as the pathogenesis of the lesion.

Key words Intestinal ischaemia · Vasculitis · Venulitis · Mesenteric veno-occlusive disease · Idiopathic enterocolic phlebitis · Enterocolic lymphocytic phlebitis

A. Corsi
Dipartimento di Medicina Sperimentale e Patologia,
Sezione di Anatomia e Istologia Patologica,
Università "La Sapienza", Rome, Italy

S. Ribaldi · M. Coletti
Istituto di Clinica Chirurgica d'Urgenza e di Pronto Soccorso,
Università "La Sapienza", Rome, Italy

C. Bosman (✉)
Dipartimento di Medicina Sperimentale e Patologia,
Università "La Sapienza", Policlinico Umberto I,
Viale Regina Elena 324, I-00161 Rome, Italy

C. Bosman
IRCCS-Ospedale "Casa Sollievo della Sofferenza",
S. Giovanni Rotondo, Foggia, Italy

Introduction

Intestinal vasculitis can occur in the context of systemic vasculitis or in association with chronic inflammatory bowel disease, mainly Crohn's disease [12]. Isolated intestinal vasculitis is extremely rare and venulitis much rarer [6].

Recently, Flaherty et al. [6] described seven patients with occlusive inflammatory disease of mesenteric veins and venules who had no evidence of extraintestinal vasculitis or other bowel diseases, and they called this condition mesenteric inflammatory veno-occlusive disease. Similarly, three patients presenting with intestinal ischaemic necrosis described as idiopathic entero-colic lymphocytic phlebitis and another described as enterocolic lymphocytic phlebitis were reported by Saraga and Costa [18] and Haber et al. [8], respectively.

We report on a case of intestinal necrosis caused by limited intramural mesenteric venulitis in a 44-year-old woman who had no clinical evidence of systemic vasculitis, systemic collagen-vascular or other bowel diseases, including thrombotic occlusion of the mesenteric vessels, and was not taking any long-term medication.

Clinical history

A 44-year-old female patient was admitted to the surgical ward after the abrupt onset of abdominal pain localized to the right lower quadrant and flank. She was not taking any long-term medication and reported no previous abdominal pain or bloody stools; nor did she show any clinical evidence of systemic collagen-vascular disease. On physical examination, pain was localized to the lower abdominal quadrants, especially the right one, both spontaneously and on palpation. Involuntary muscle guarding, direct rebound tenderness, increased peristalsis and visceral tympanism were present. Within 24 h the patient developed nausea and vomiting, without fever or stool disorders. Laboratory findings showed moderate leucocytosis (11,300/mm^3), with neutrophils predominant (76.8%). Radiological findings included distension of the small intestine. Because of the clinical condition, the patient underwent urgent surgery. The caecum and the ascending colon were purplish and deformed, with a thickened wall, and a right hemi-colectomy was performed.

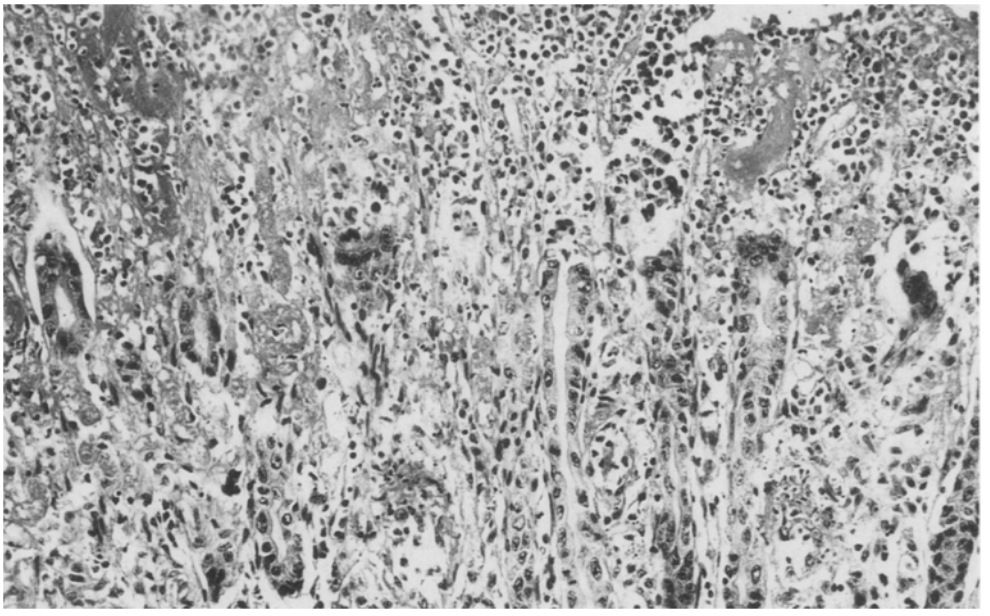

Fig. 1 Ischaemic lesion of the intestinal mucosa, characterized by necrosis of glandular and lining epithelium and haemorrhages and capillary thrombosis in the lamina propria. ×110

The post-operative recovery was optimal and the patient was discharged 9 days later. No clinical or laboratory abnormalities were found 1, 3 and 7 months after surgical treatment.

Materials and methods

Multiple specimens of the resected bowel, from necrotic and grossly uninvolved areas, and from the mesenteric tissue, including extramural mesenteric veins, were fixed in 4% buffered formaldehyde and embedded in paraffin. From each block, 6-μm-thick sections were cut and stained with haematoxylin-eosin, Verhoeff-Van Gieson stain for elastic tissue, Ziehl-Nielsen stain for acid-fast bacilli, Gram's stain for bacteria and Gomori's ammoniacal silver stain for fungi.

In addition, immunohistochemical study was carried out using an indirect immunoperoxidase protocol. Dewaxed and hydrated sections were treated with 0.4% hydrogen peroxide in absolute methanol (15 min at room temperature) to block endogenous peroxidase activity and with normal rabbit serum for 20 min to reduce background staining. Two primary antibodies were used for lymphocytic typing: monoclonal L26 (CD20) against human B cells (Dako) and monoclonal UCHL1 (CD45Ro) against human T cells (Dako), both at the dilution of 1:50, for 1 h at room temperature. Sites of antibody binding were revealed with a peroxidase-conjugated rabbit anti-mouse immunoglobulin antiserum (Dako) at the diluition of 1:25, for 30 min at room temperature. The colour reaction was performed with 3,3'-diaminobenzidine tetrahydrochloride (DAB) in the presence of hydrogen peroxide. The sections were counterstained with Harris' haematoxylin. Negative controls consisted of sections stained with non-immune rabbit serum in lieu of primary antibodies. Sections of tumours known to contain the determinants of interest served as positive controls.

Pathological findings

The resected bowel was enlarged with thickening of the wall, loss of the normal haustra, purple colour and confluent superficial ulcerations of the mucosa, mainly in the caecum. Extramural mesenteric veins were dilated and congested.

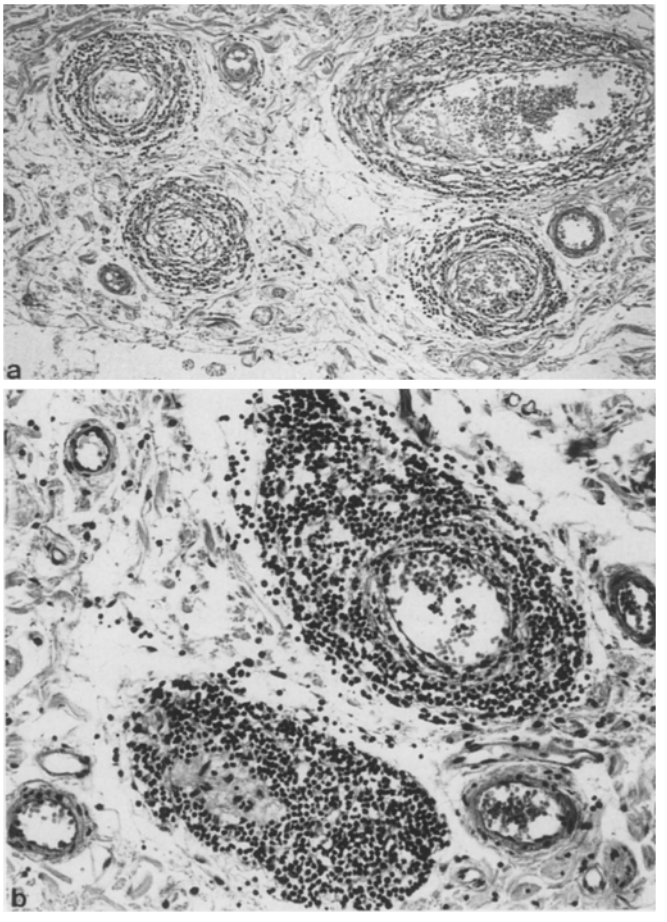

Fig. 2 **a** Inflammatory lymphocytic venulitis in the submucosal venous vessels without involvement of arteriolar vessels. ×20. **b** Higher magnification showing the infiltrate involving all layers of the venular wall and extending into the connective perivenular tissue. ×80

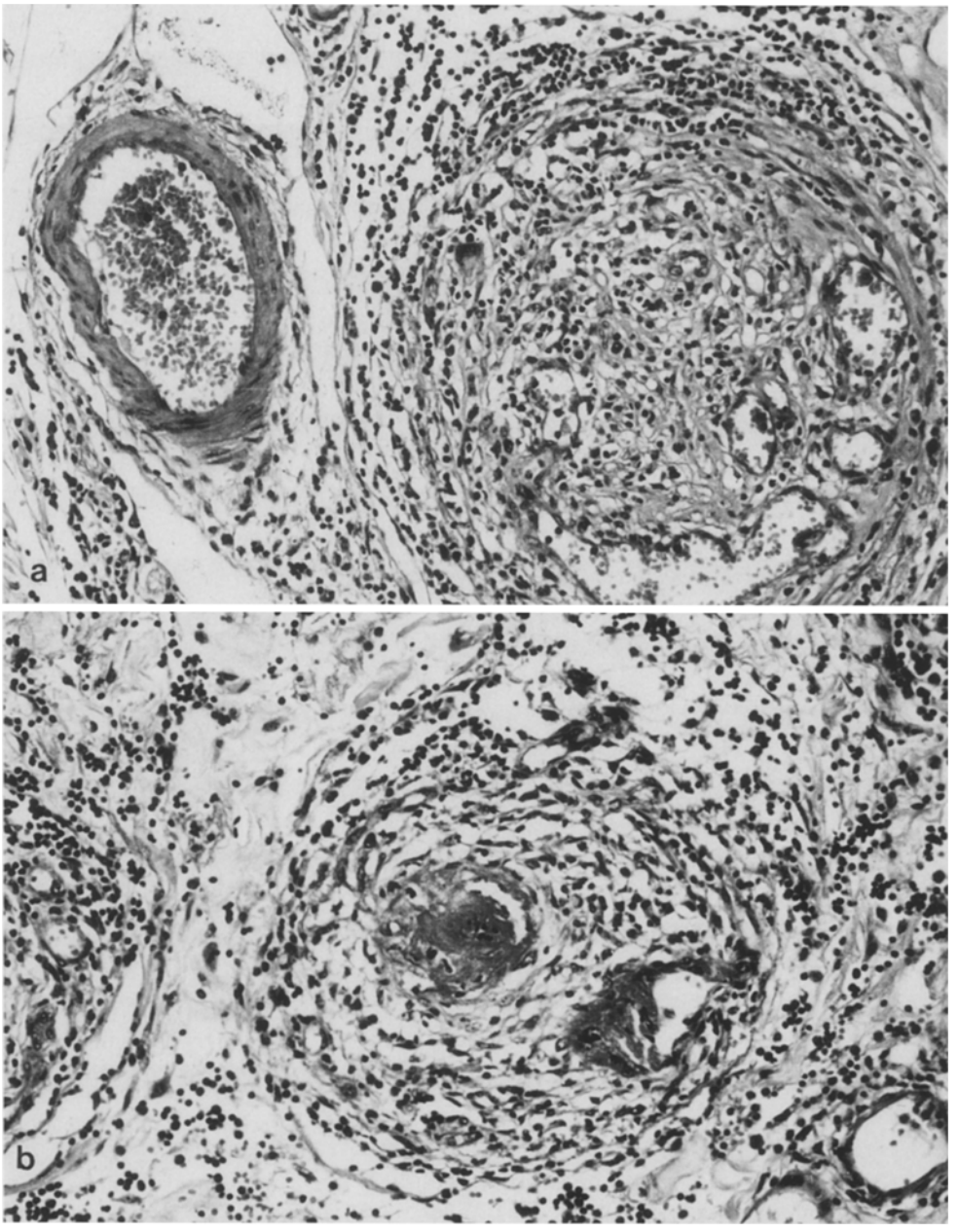

Fig. 3a, b Venular thrombi of different ages. **a** Old and organized thrombus with recanalization of the lumen. ×120. **b** Recent sub-occlusive thrombotic lesion. ×120

Histological examination showed degrees of ischaemic injury variable from area to area. Mild and superficial lesions were characterized by haemorrhages and oedema in the lamina propria, coagulative necrosis of the superficial and glandular epithelium, with focal formation of pseudomembranes, and thrombi in capillaries (Fig 1). Severe injured areas showed features of transmural infarction with massive venous congestion. No haemosiderin-laden macrophages were observed. The most striking feature was an inflammatory infiltrate made up of lymphocytes in the perivenular tissue and the wall of intramural tributaries of the mesenteric veins (Fig 2); arterial and arteriolar lesions were not identified. Thrombotic lesions of different age were found diffusely (Fig 3 a,b). Lymphocytic venulitis was also present at the resection margins. Extramural mesenteric veins appeared dilated and markedly congested, without histological evidence of thrombotic occlusion or inflammatory infiltrate in their wall. Stains for microorganisms were negative and no granulomatous foci or myointimal hyperplasia were noted.

Immunohistochemical study revealed that the venular lymphocytic infiltrate was made up almost completely of T lymphocytes (Fig 4a); among them, a few and sparse B lymphocytes were recognized (Fig 4b).

Discussion

Intestinal ischaemia has a number of causes, among which occlusion of the mesenteric arteries and veins, nonocclusive splanchnic spasm and vasculitis are the

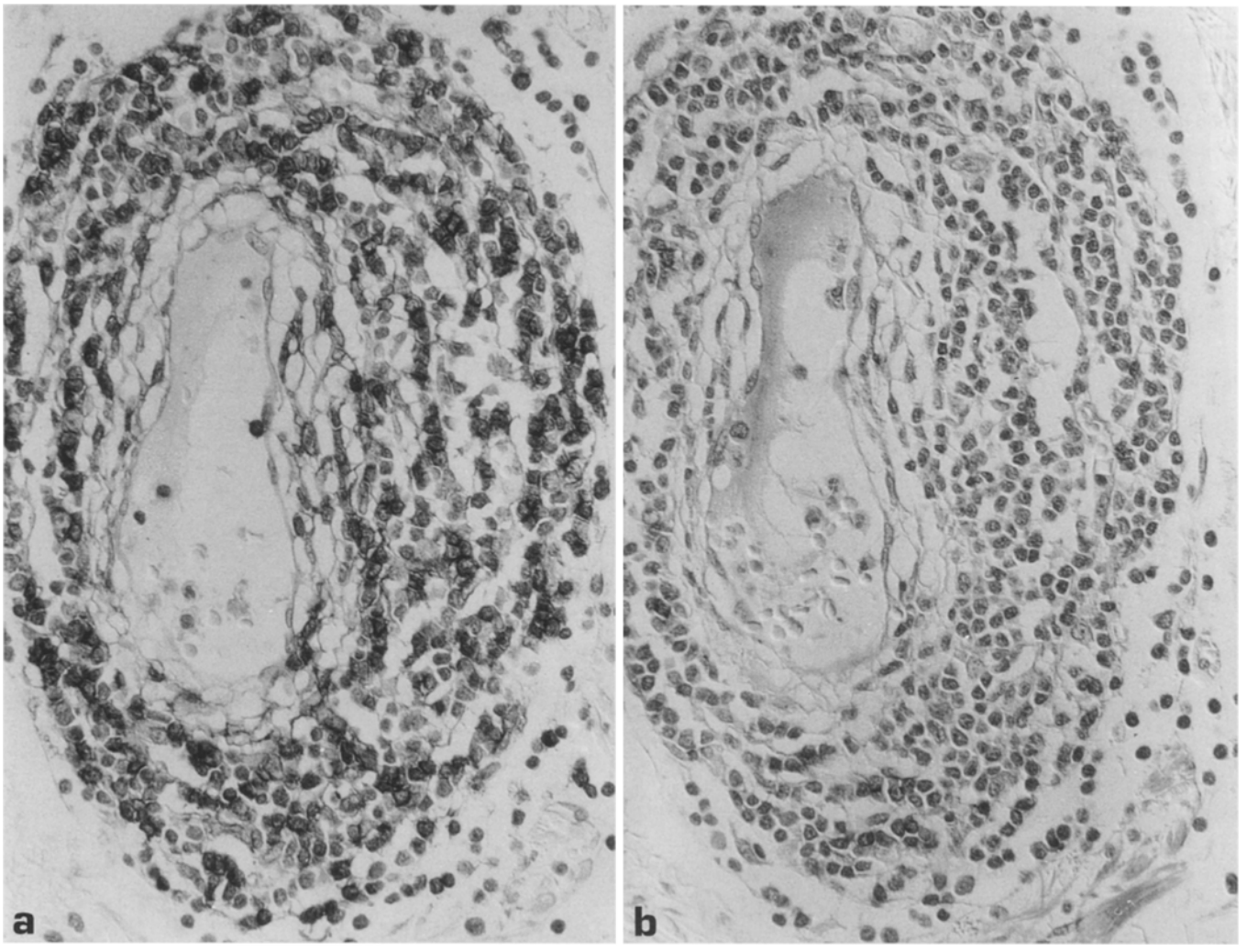

Fig. 4a, b Immunohistochemical stains with monoclonal UCHL1 against **a** human T cells (×320) and **b** monoclonal L26 against human B cells (×320). Note the marked preponderance of T lymphocytes (Nomarski)

most frequent [18]. However, intestinal vasculitis is rare and intestinal venulitis is much rarer [6]. When intestinal vasculitis occurs, it usually accompanies systemic vasculitis or chronic inflammatory bowel disease, mainly Crohn's disease, and the arterial system is primarily affected [3,12]. Intestinal ischaemia for mesenteric nonthrombotic occlusion has been described in Churg-Strauss syndrome and Behçet's disease [10,13]; intestinal venulitis has been described in systemic lupus erythematosus [9,17,22], Behçet's disease [1,10,15], rheumatoid arthritis [19], Buerger's disease [11], and in drug-related vasculitis [14]; in all these conditions venular involvement coexists arterial vasculitis and extra-intestinal manifestations are usually present.

In extraintestinal sites, limited venulitis has been described in alcoholic liver disease, in which myointimal hyperplasia was also present [2,7], in the retina of patients with multiple sclerosis [5], in the lung [4] and in the central nervous system [16].

Flaherty et al [6] described mesenteric inflammatory veno-occlusive disease, a limited vasculitis of mesenteric veins and its intramural tributaries causing intestinal ischaemia. Their patients, four women and three men, ranged in age from 27 to 78 years, complained of abdominal pain and discomfort for a period ranging from 1 week to several months (nausea, vomiting and bloody stools were present in some of the patients) and were treated by segmental resection of the ischaemic bowel. Follow-up, which varied in duration from 6 to 18 months, was free from local recurrences and systemic signs and symptoms; one of the patients died one month after surgery from causes not related to the disease. Histology of the resected bowel showed lymphocytic (4 cases), lymphocytic and granulomatous (1 case) or necrotizing (2 cases) vasculitis of mesenteric veins and their intramural tributaries without arterial and arteriolar involvement, and myointimal hyperplasia (3 cases).

Other similar cases have been reported. VanWay et al. [21] described necrotizing venulitis in three of five patients with unexplained mesenteric vein thrombosis. Necrotizing and granulomatous phlebitis of the caecum and ascendent colon was described by Stevens et al. [20] in a 36-year-old woman undergoing right hemicolectomy for

intestinal ischaemia. Saraga and Costa [18] described idiopathic enterocolic lymphocytic phlebitis in three adult patients with intestinal ischaemia, all of whom were receiving topical treatment with hydroxyethil rutoside for varicose veins; in these patients, even if involvement of mesenteric veins was present, focal fibrinoid necrosis, marked and extensive lymphocytic infiltrate, and thrombi of different ages were more conspicuous in the intramural submucosal venous vessels. Immunohistochemical stains revealed predominance of T and B lymphocytes in the inner and outer zones of the venous wall, respectively. A similar picture, with a mixed T- and B-cell vasculitis affecting veins in the wall and mesentery of the bowel, has been recently described as enterocolic lymphocytic phlebitis by Haber et al. [8].

In the case reported here, histological examination of the resected colon showed intense lymphocytic infiltrate in perivenular tissue and intramural venular walls, with frequent obliteration of the lumen by thrombi of different ages, without arterial and arteriolar involvement. No microorganisms, granulomatous foci, necrotizing angiitis or myointimal hyperplasia were found. Extramural mesenteric veins, although markedly congested, did not show histological evidence of thrombotic occlusion or lymphocytic phlebitis. Immunohistochemical study revealed a marked predominance of T cells in the lesion. In the absence of other potential causes, we think that the intestinal ischaemia was due to extensive thrombotic lesions induced by the intramural lymphocytic venulitis. Organized thrombi indicate that the acute episode might have been precipitated by the formation of fresh thrombi as the venular lesions have a subacute or chronic evolution. However, it should be noted that, in spite of the evidence of organizing venous thrombi in the pathology specimens, our case appears quite unusual in the short duration of the clinical history.

Based on the comparative morphological features of our case and those in the literature, we suggest a new spectrum of diseases causing intestinal ischaemia; this seems to range from mesenteric inflammatory veno-occlusive disease [6], in which main and intramural mesenteric veins were equally involved, at one extreme, through idiopathic enterocolic lymphocytic phlebitis [18], in which intramural venous vessels were mainly, but not exclusively, involved, to the lesion that occurred in our patient, in which intramural veins were involved exclusively, at the other extreme; the lesion reported by Haber et al. [8] can also be included in this spectrum. These lesions may be related to each other and represent the expression of the same pathological process, possibly in different phases of development. While the aetiology is unknown, histology and immunohistochemical data suggest lymphocyte-mediated vascular damage in the pathogenesis of the lesion [18]. Only the three patients of Saraga and Costa [18] were exposed to hydroxyethyl rutoside.

The absence of extramural mesenteric venous involvement (a distinctive feature in this case) suggests that intramural mesenteric venulitis could represent the intramural phase, or "microscopic" variant, of this new spectrum of diseases causing intestinal ischaemia.

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