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Clinical Case Report

Enterocolic lymphocytic phlebitis with marked myointimal hyperplasia and perivenous concentric fibrosis☆,☆☆

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ABSTRACT

Enterocolic lymphocytic phlebitis (ELP) is a rare enteropathy characterized by lymphocytic phlebitis of the mesenteric veins without arteritis. Idiopathic myointimal hyperplasia of mesenteric veins (IMHMV) is a rare disease similar to ELP, characterized by myointimal hyperplasia that constricts the lumen of veins, causing mucosal injury. A 62-year-old man with chief complaint of abdominal pain was treated by partial resection of the ileum after 3 months of conservative therapy. The pathologic diagnosis was ELP with prominent myointimal hyperplasia. Histologically, the lesion consisted of lymphocytic infiltration into the vein accompanied by prominent myointimal hyperplasia and perivenous concentric fibrosis, which are characteristics shared by ELP and IMHMV. The observations in this case suggest that some of ELP and IMHMV may belong to the same disease spectrum. Furthermore, perivascular concentric fibrosis was a remarkable observation that may contribute to differential diagnosis between ELP and "true" IMHMV.

1. Introduction

Enterocolic lymphocytic phlebitis (ELP) is a rare enteropathy associated with intestinal congestive injury caused by lymphocytic infiltration into the mural and mesenteric veins [1–4]. In ELP, veins of various sizes, but not arteries, are affected by lymphocytes. ELP in mesenteric veins is rarely accompanied by myointimal hyperplasia [1–4]. Idiopathic myointimal hyperplasia of mesenteric veins is a rare disease similar to ELP characterized by myointimal hyperplasia that constricts the lumen of veins causing mucosal injury and ulcers. Previous reports have suggested that idiopathic myointimal hyperplasia of mesenteric veins (IMHMV) and ELP may belong to the same disease spectrum [5,6]. Here, we present a case of ELP with prominent myointimal hyperplasia and concentric fibrosis around veins surgically resected following unsuccessful conservative treatment for 4 months.

2. Case report

A 62-year-old man presented to a clinic with abdominal pain 3 months before his first admission to our hospital. His medical history included hypertension, cerebral infarction, and atrial fibrillation, and he had received anticoagulation therapy and antihypertensive therapy. He did not have any family histories of gastrointestinal disorders. He was an ex-smoker (10 pack-years). In the clinic, colonoscopy did not result in specific findings, including anal lesions, and the patient was conservatively treated. However, the patient's symptoms did not improve, and the small bowel became dilated, as shown by examination using abdominal radiography. Following this result, he was referred to our hospital. Physical examination revealed right lower abdominal pain, with no skin rash or edema. Laboratory investigations indicated increased inflammation and normal renal function, with results as follows: white blood cell (WBC) counts, 8700 cells/μL (normal: 3100–9500 cells/μL); C-reactive protein (CRP), 10.0 mg/dL (normal: <0.3 mg/dL); blood urea nitrogen, 11.0 mg/dL (normal: 7.2–20.0 mg/dL); creatinine, 0.85 mg/dL (normal: 0.50–1.10 mg/dL); prothrombin time-international normalized ratio, 1.10 (normal: 0.85–1.15); activated partial thromboplastin time, 30 s (normal: 24–38 s); and anti-nuclear antibodies, negative. Anti-neutrophil cytoplasmic antibody was not examined because he had no skin rash, renal dysfunction, or pulmonary

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nodules. Contrast-enhanced abdominal computed tomography (CT) showed wall thickening with a 10 cm localized contrast enhancement in the distal ileum, dilation of the proximal intestinal tract, and increased density of mesenteric fatty tissue (Fig. 1A). Except for the mesenteric lesion, no findings that suggested vasculitis were detected in the chest to pelvis region. Arterial or venous thrombosis was also not observed. Colitis, such as Crohn's disease, was initially suspected. The patient was fasted, and given intravenous fluids and antibiotics. Abdominal pain and inflammatory status improved (WBC, 8400 cells/μL and CRP, 3.9 mg/dL). However, 2 weeks after the initial visit at our hospital, contrast-enhanced abdominal CT showed exacerbation of small intestinal stenosis. Thus, partial resection of the ileum was performed 4 months after presentation of initial symptoms.

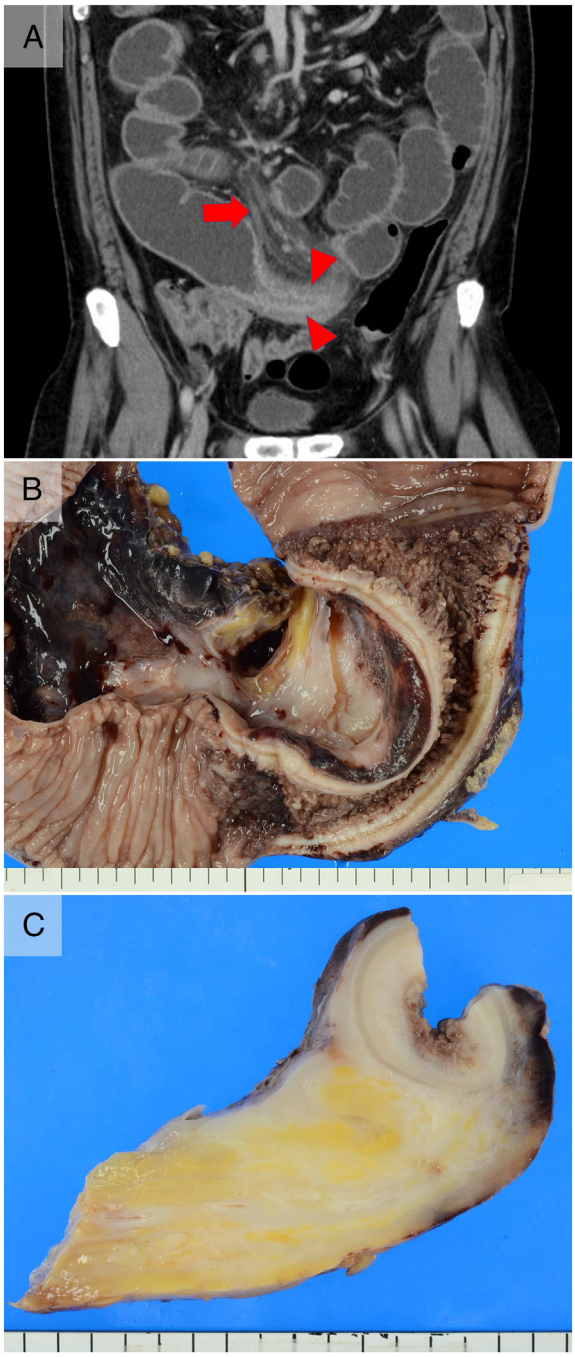

Fig. 1. Radiographic and macroscopic appearance of the lesion. (A) Contrast-enhanced computed tomography showed thickened enteric wall with localized contrast effect in the distal ileum extending 10 cm in length (arrowheads). Proximal intestinal tract was dilated, and density of the surrounding mesenteric fatty tissue increased (arrow). (B) Gross appearance of the resected specimens. The mucosal surface showed villous structures with a thick intimal axis, and a well-circumscribed brownish stenotic area was observed. (C) On the cut surface of the brownish lesion, a whitish area consistent with fibrosis spread from the muscularis propria to the subserosal tissue.

The resected specimens underwent pathological examination. In gross appearance, a 125 mm well-circumscribed circular brownish region accompanied by stenosis was observed in the ileum. The mucosal surface had a thick villus-like structure (Fig. 1B). The intestine in the region proximal to the brownish stenotic area was expanded. Longitudinal ulcers were not found. On the cut surface of the brownish lesion, a whitish area consistent with fibrosis spread from the muscularis propria to the subserosal lamina (Fig. 1C).

Histologically, prominent subserosal fibrosis was present in the lesion, in which veins showed myointimal hyperplasia, consisting mainly of muscular hyperplasia, resulting in narrowing of the intravenous lumens (Fig. 2A). Concentric fibrosis around the affected veins was also observed (Fig. 2B, C). In some places, lymphocytic infiltration into the venous wall was observed, which led to a diagnosis of phlebitis. The outer diameter of the affected veins, limited to the subserosal tissue, was 200 to 1000 μm. Arteries were unaffected.

In the mucosal layer of the lesion, erosion was conspicuous. In some parts, ulcers abutting the internal layer of the muscularis propria and prominent neutrophilic infiltration were also observed. The villous interstitium was broadened and accompanied by dilatation of capillary vessels, and the walls of these vessels were thickened similar to arterioles (Fig. 2D). Hyalinization of small blood vessels, which suggests idiopathic mesenteric phlebosclerosis, was not observed. Crypt architectural distortion was observed at the periphery of the lesion (Fig. 2E). Congestion was observed in the submucosal layer. No carcinoma, malignant lymphoma, or granulomatous lesion, characteristics of Crohn's disease, were observed. Immunohistochemistry revealed that the lymphocytes that infiltrated into the vein were mainly CD3+ (clone PS1, working dilution 1:100; Leica Biosystems) T-cells (Fig. 3A). B-cells positive for CD20 (clone L26, working dilution 1: 100; Leica Biosystems) were only sparsely present (Fig. 3B). CD4+ (clone SP 35, working dilution 1: 100; Cell Marque Corporation) T-cells were more abundant that CD8+ (clone C 8/144 B, working dilution 1: 100; Dako) T-cells (Fig. 3C, D). IgG4+ (clone HP 6025, working dilution 1: 100; Southern Biotech) cells were rarely observed.

Because this lesion presented as phlebitis without arteritis accompanied by concentric fibrosis around the veins, suggesting chronic inflammation, we diagnosed it as an ELP with prominent myointimal hyperplasia.

After surgery, symptoms such as abdominal pain and radiological abnormalities improved, and the patient was discharged without serious complications on postoperative day 32. He was followed as an outpatient for one year following the procedure without any relapse of symptoms or recurrence on CT imaging.

3. Discussion

We presented a case of ELP with prominent myointimal hyperplasia and concentric fibrosis around the affected veins. Although lymphocytic infiltration into venous walls was less evident than that in a typical ELP case, we assigned a diagnosis of ELP because concentric fibrosis around the veins was consistent with prolonged phlebitis, and arteritis was not observed.

ELP is an enteropathy caused by phlebitis [1,7]. Patients with ELP typically present with acute abdominal pain, nausea, vomiting, diarrhea, or rectal bleeding, often accompanied by an underlying disease, such as cardiovascular disease, hypertension, renal failure, or malignancy [1,6]. ELP typically affects the small intestine or right-sided colon [1,6]. No specific endoscopic or radiological findings have been associated with ELP [1]. Histologically, veins of all sizes within the intestinal wall can be affected by lymphocytes, predominantly T-cells, but the arteries are never affected [1].

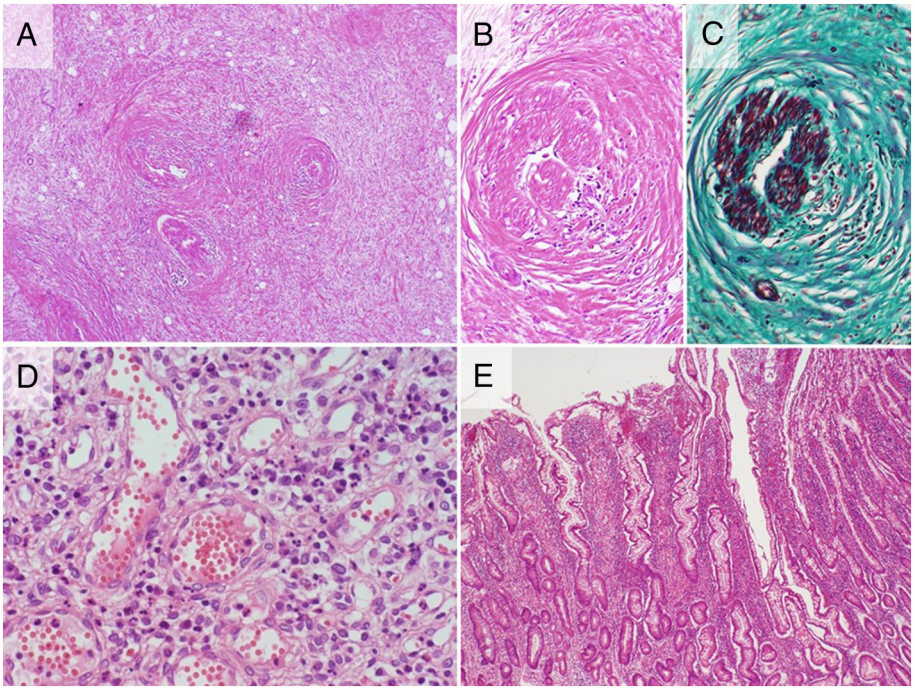

Fig. 2. Histology of the lesion. (A) The veins showed myointimal hyperplasia, consisting primarily of muscular hyperplasia, resulting in narrowing of the intravenous lumens. (B, C) Concentric fibrosis around the affected veins was also observed using hematoxylin–eosin stain (B) and elastica-Masson stain (C). (D) The walls of the mucosal capillaries in the villi were thickened similar to arterioles. (E) Crypt architectural distortion was seen in the periphery of the lesion (arrowheads).

IMHMV, an enterocolic venous disease similar to ELP, is histologically characterized by narrowing of the mesenteric venous lumen caused by myointimal hyperplasia [5,6]. Patients with IMHMV typically seek medical attention several months after experiencing abdominal pain or bloody stools. Furthermore, IMHMV is typically not accompanied by an underlying disease, and the left-sided colon is commonly affected [5,6]. Indeed, the name "mesenteric inflammatory veno-occlusive disease" was originally used for ELP, and the two entities, ELP and IMHMV, were classified under the same category in the past; however, they are now recognized as separate diseases because of the differences of their clinical courses [4,5]. In the present case, clinical features supported a diagnosis of ELP. However, myointimal hyperplasia was prominent in this patient. Some cases of ELP with myointimal hyperplasia have been reported. In these cases, the time from initial symptoms to surgery tends to be relatively long, typically several months [1,5,6,8,9]. In the present case, the patient underwent surgical

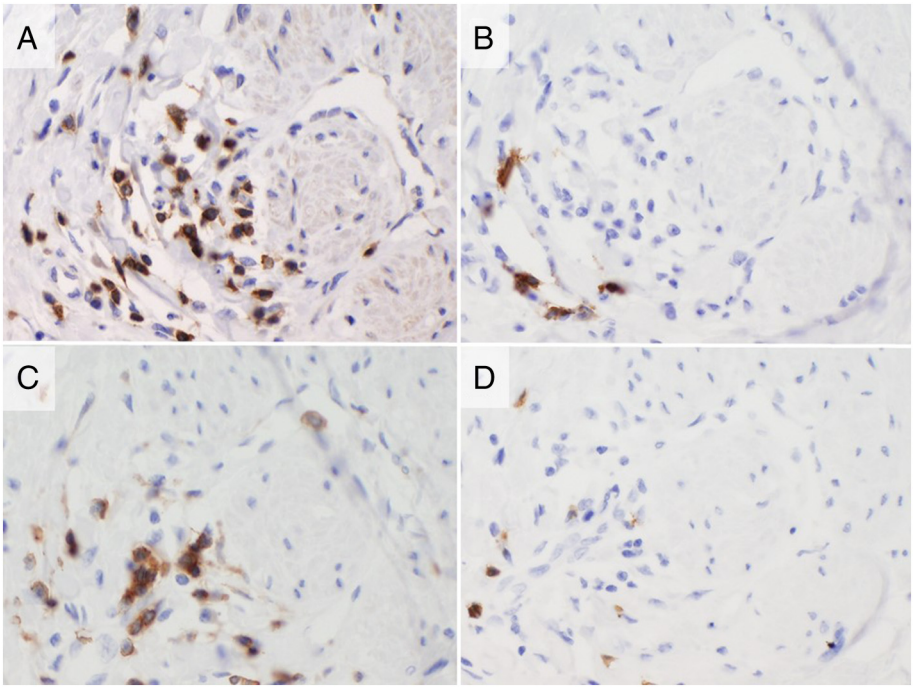

Fig. 3. Immunohistochemistry of lymphocytes that infiltrated into the veins. (A) Lymphocytes that infiltrated into the veins were mainly CD3+ T-cells. (B) Few CD20+ B-cells were observed. (C, D) CD4+ T-cells (C) were more abundant than CD8+ T-cells (D).

intervention 4 months after onset of symptoms. Mild lymphocyte infiltration with concentric fibrosis around the vein suggested a chronic disease course. A recent study reported histological characteristics of IMHMV including arteriolized capillaries, ulceration, and regenerative microcrypts [5,6]. In our patient, we observed ulceration, capillaries with thickened walls, and crypt distortion, similar to the previously reported characteristics of IMHMV. Because these findings seemed to reflect congestive changes of blood vessels and mucosal injury due to venous occlusion, they could also be consistent with ELP.

Concentric fibrosis around the veins may be a key finding in chronic ELP. The pathological difference between ELP and IMHMV is the presence or absence of phlebitis. However, lymphocyte infiltration was relatively mild in chronic ELP. Perivenous concentric fibrosis may suggest chronic inflammation of veins. Although no studies have focused on concentric fibrosis around the veins, a figure in a previous case report on ELP with a long clinical course before surgery showed concentric fibrosis similar to that observed in our case [8]. Concentric fibrosis around the veins may allow for pathological differentiation between chronic ELP and "true" IMHMV without past inflammation. Further studies focusing on this finding are expected in the future.

Although the difference between ELP and IMHMV is unclear [1–6,8,9], some diagnoses of IMHMV may have been ELP resected after a long clinical course. As there are clinical differences between ELP and IMHMV, it is difficult to regard them as the same disease. However, in all reports of IMHMV of the small intestine, resection occurred after several months [5,6,9], suggesting that venous damage observed in IMHMV cases may have been due to chronic ELP. In addition, some patients with IMHMV were treated with anti-inflammatory drugs such as steroids, which might diminish inflammatory findings. The present case was diagnosed as ELP with myointimal hyperplasia with a long clinical course before surgery. Mucosal injury and changes in capillaries accompanying congestion were similar to IMHMV [5]. Thus, some cases diagnosed as IMHMV might be on the same spectrum as chronic ELP [9].

Some case reports have identified infiltrating lymphocytes in ELP as T-cells, despite absence of systematic immunohistochemical analysis [1,3,10]. In this case, lymphocytes that had infiltrated into the veins were primarily CD3+ T-cells rather than CD20+ B-cells, which was consistent with previous reports [1,3,10]. In contrast, a case report published more than 15 years ago reported that CD4 negative T-cells were predominant in ELP [3]. The anti-CD4 monoclonal antibody used in this previous report was different from that used in our case study, which may explain different CD4 expression results. In giant cell arteritis, Takayasu arteritis, Granulomatosis with polyangiitis, Buerger's disease, and necrotizing vasculitis seen in pulmonary hypertension, CD4+ T-cells predominantly infiltrate into the vasculature compared to CD8+ T-cells [11–15]. As ELP is a kind of vasculitis, it seems reasonable that veins are also affected mainly by CD4+ T-cells in ELP. The predominant type of T-cells in ELP, whether CD4+ or CD8+, should be adequately investigated in future studies.

In conclusion, we described a case of ELP with prominent myointimal hyperplasia, which shared characteristics of both ELP and IMHMV, suggesting that IMHMV may belong to the same disease spectrum as chronic ELP. Furthermore, perivascular concentric fibrosis in this case was a remarkable observation that has not received previous attention. This finding may provide a basis for differential diagnosis between ELP and "true" IMHMV.

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