Enterocolic Lymphocytic Phlebitis
Clinicopathologic Features and Review of the Literature

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Enterocolic lymphocytic phlebitis (ELP) is a recently described entity and is of unknown etiology and pathogenesis. It is characterized by phlebitis of the bowel wall and mesentery, without arterial involvement or evidence of systemic vasculitis. The clinical presentation of ELP is varied, but it most commonly manifests with signs of an acute abdomen. Clinical, radiologic, and endoscopic findings are often conflicting and misdiagnosis is common as venous thrombosis is not suspected. The diagnosis of ELP is obtained histologically. There is a spectrum of histologic features associated with ELP, which includes lymphocytic phlebitis, necrotizing phlebitis, granulomatous phlebitis, and myointimal hyperplasia. Other features include venous thrombi and acute ischemic changes of the intestine. Surgical resection of the affected bowel is usually curative and recurrences are rare. The clinical and histopathologic features of ELP are reviewed.

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Intestinal vasculitis is frequently seen as part of a systemic vasculitis, whereas the occurrence of localized vasculitis in the gastrointestinal tract in the absence of systemic involvement is uncommon. This latter type of vasculitis is often associated with inflammatory bowel disease, for example, Crohn disease, and involves mainly the arteries. Isolated intestinal venulitis is extremely rare. To our knowledge, fewer than 50 patients have been reported in the English literature.

The first case was reported by Stevens et al in 1976 who described necrotizing and granulomatous phlebitis of the large bowel in a previously healthy woman. Subsequently, Saraga and Costa coined the term enterocolic lymphocytic phlebitis (ELP) in a case series of 3 patients in 1989. This term is synonymous with mesenteric inflammatory veno-occlusive disease, intramural mesenteric vasculitis, isolated granulomatous phlebitis, lymphocytic venulitis, idiopathic myointimal hyperplasia of mesenteric veins, and necrotizing and giant cell granulomatous phlebitis. Since the original reports, more cases of ELP have arisen. This article focuses on characterizing the clinicopathologic aspects of this condition.

CLINICAL FEATURES OF ELP

In this review, ELP was found in 16 men (47%) and 18 women (53%). The median age of diagnosis was 63 years. Twenty-seven (79%) of the patients were older than 50 years old and the youngest patient to be diagnosed was 25 years old.

None of the patients had a history of systemic vasculitis...
and there was no drug in common in their medications. Approximately 68% of the patients had associated disease. The most common of these include cardiovascular disease, hypertension, malignancies, and renal failure.2–30

The pathogenesis of the disease is not known. However, in 1989, Saraga et al.5 described a series of 3 patients with intestinal ischemia caused by ELP that was thought to be associated with the use of hydroxyethyl rutoside (Venoruton), a phlebotonic drug used in Europe for varicose veins. This association with rutoside was also found by Chergui et al.27 Another drug that has been associated with ELP is the antiandrogen drug flutamide.11,24

Patients with ELP most commonly present with signs of acute abdomen, which manifest as acute abdominal pain, nausea and vomiting, diarrhea, and/or rectal bleeding.2,3,5–7,13–18,22–27 In 14 patients,7,13,15,19,22,25 there were prodromal symptoms, predominantly abdominal pain, lasting weeks to years in 1 reported case.2 Five of the patients presented with abdominal mass, which resembled carcinoma both clinically and radiologically.14,21,23,28 This has been attributed to the edema and inflammation associated with venous outflow obstruction, which would produce similar clinical features.15

According to the literature, there does not appear to be any specific endoscopic or imaging findings that would indicate a diagnosis of ELP. However, computed tomography scanning and/or transabdominal ultrasonography in 7 patients showed thickened and edematous bowel walls.3,7,14–16,21,24 Lavu and Minocha7 suggested the use of mesenteric angiography to distinguish ELP from inflammatory bowel disease. According to their observation, local mesenteric hypervascularity with ectatic vessels may suggest inflammatory bowel disease, whereas the absence of draining veins from the involved segments favors the diagnosis of ELP.

All the patients were refractory to medical treatment and surgical exploration was undertaken. Surgical resection of the affected bowel is usually both diagnostic and curative without any recurrences. The rare exceptions are a patient who had a histologically confirmed recurrence of ELP requiring surgical resection22 and another patient who had recurrent phlebitis on biopsy but did not require further surgery.2 There are also 2 reports of rapid postoperative deaths, which may be due to overwhelming mesenteric ischemia.19,20 Follow-up of these patients ranged from 6 months to 15 years, and no evidence of systemic vasculitis was found in any of the patients.

**PATHOLOGIC FEATURES OF ELP**

Enterocolic lymphocytic phlebitis lesions are mostly located either in the large or small bowel. Enterocolic lymphocytic phlebitis was found only in the large bowel in 17 cases, predominantly right colon (9 cases).9 It was noted

*References 2, 6, 7, 9, 10, 14–16, 18, 19, 21, 25, 26, 28, 29.*
in both right colon and ileum in an additional 6 cases. Being a part of the colectomy specimens, the appendix was involved by ELP in 4 cases. Abraham et al. described a case of lymphocytic phlebitis that affected only the upper gastrointestinal tract, that is, the stomach and duodenum.

Of 26 cases for which gross examination was available, 15 cases showed intestinal infarction. 5 cases showed thickening of bowel wall. 3 cases showed tumorlike mass, and 2 cases showed ulceration. In 1 case, the bowel was macroscopically normal except for a cecal diverticulum.

One of the main histologic characteristics of ELP is the distinctive vascular changes. The arteries are invariably uninvolved, whereas the veins show prominent lymphocytic inflammation affecting veins of all sizes, including intramural venules (Figure 1, A) and small veins (Figure 1, B) of the intestine as well as large mesenteric veins (Figure 1, C). The involved vessels are often located in the bowel wall, particularly in the submucosa (17 cases). Saraga and Bouzourenne also observed that the inflammatory changes were more significant in smaller sized venules (<2 mm in diameter).

The hallmark of ELP is the presence of lymphocytic phlebitis, as described by Saraga et al. This feature is found in all the case reports and is usually the predominant type of inflammatory response. It is characterized by diffuse lymphocytic infiltration of the venular wall and dense perivenular infiltrate forming lymphocytic cuffs of variable thickness (Figure 1, A through C). This cuff of small uniform-appearing lymphocytes with occasional plasma cells and rare eosinophils is usually concentric, sometimes eccentric (Figures 1, A through C, and 2, A). Immunohistochemistry performed on 11 cases revealed marked preponderance of perivenular CD3+ T lymphocytes (Figure 2, B). Only occasional cells are B lymphocytes (Figure 2, D). This may suggest lymphocyte-mediated vascular damage. Abraham et al. and Tuppy et al. noted that the majority (>90%) of T cells were CD8+ (Figure 2, C) and approximately half of these had intracytoplasmic T-cell restricted intracellular antigen (TIA-1) granules indicating a cytotoxic phenotype.

Other types of phlebitis include necrotizing phlebitis characterized by infiltration of the vessel walls by polymorphonuclear leukocytes and fibrin deposition (Figure 3, A). This was the dominant pattern of phlebitis in 6 cases. Granulomatous phlebitis with epithelioid histiocytes and multinucleated giant cells was found in association
with lymphocytic phlebitis in 6 cases and was the minor component of the phlebitis (Figure 3, B). Endothelial and myointimal hyperplasia with near complete occlusion of vessel lumen (Figure 3, C) was seen in 10 cases and was the predominant pattern in 2 patients. Another striking histologic feature associated with ELP was the presence of fresh and/or organized venous thrombi (Figure 3, D) in 23 cases. In 19 of these 23 cases, hemorrhagic transmural ischemic infarction was present. The mechanism underlying intestinal ischemia may be due to venous thrombi occurring as a complication of venous inflammation. The venous thrombi consequently result in marked venous congestion, which leads to significant edema and compression of tissue and consequently necrosis.2,24

Several authors noticed that microscopic changes of ELP were found at surgical resection margins, although these margins appeared macroscopically normal.2,5,15,26 There is 1 documented recurrence, which may be the result of inadequate resection rather than a recurrence.22 However, it appears to be difficult to ascertain the extent of the disease macroscopically at the time of the operation, unless ELP was suspected and a frozen section of the margins was performed. In 1 case reported by Bao et al,15 the patient underwent a second operation for colostomy takedown after the initial resection that showed ELP. This second specimen showed no evidence of ELP. This would support the theory of resolution of ELP after resection.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

It appears that, on reviewing the literature, all of the reported ELP cases are presented with an artery-sparing vasculitis limited to the gastrointestinal tract, with obvious phlebitis in viable and ischemic portions of resected bowel.5–30 The involvement of the small bowel and/or of different segments of the colon indicates that veins in both the superior and inferior mesenteric circulation may be involved.

The presenting feature of this disease is subacute to acute visceral ischemia manifested as abdominal pain, hematochezia, and bloody diarrhea. Patients often first come to the attention of gastroenterologists, and a workup for inflammatory bowel disease is initiated. All reported cases have proved refractory to medical management, with persistent symptoms or findings of acute abdomen prompting surgical exploration.

On histologic examination, ELP shows a large spectrum of venous lesions, including lymphocytic infiltration of the venular wall (Figure 1, A through C), necrotizing phlebitis (Figure 3, A), granulomatous phlebitis (Figure 3, B), and endothelial and myointimal hyperplasia (Figure 3, C). In surgically resected specimens, the affected bowel often shows ischemic changes ranging from ischemic colitis to transmural hemorrhagic infarction (Figure 4, A through C). Endoscopic biopsies of the affected bowel may show features of ischemic colitis (Figure 4, A), ulceration, and mucosal necrosis (Figure 4, B). Saraga and Bouzourenne2 suggested that ELP may be a lymphocyte-mediated vascular damage linked to a hypersensitivity reaction. Lymphocytic phlebitis may represent the early stage of the venous lesions, whereas organized venous thrombi and myointimal hyperplasia with resolution of inflammation may represent the other end (end-stage) of the spectrum. As the endoscopic or imaging findings are often nonspecific, the diagnosis of ELP remains largely a pathologic diagnosis based on findings of mesenteric venulitis, uninvolved arteries, and venous thrombosis.

Enterocolic lymphocytic phlebitis is usually not associ-
ated with other forms of colitis. However, Arora et al\textsuperscript{11} reported a case of lymphocytic phlebitis that was found proximally and overlapped with collagenous and lymphocytic colitis found distally. In addition, Wright and Cacala\textsuperscript{24} reported a similar case with features of lymphocytic colitis with an excess of intraepithelial lymphocytes. The patients in these 2 cases were exposed to flutamide, which may be the triggering factor. Phenotypically, T lymphocytes are the main cell type of the inflammatory infiltrate in both ELP and lymphocytic colitis, thus these 2 disorders may be casually related.

The differential diagnosis includes mesenteric vasculitides and/or thrombosis associated with systemic vasculitides such as systemic lupus erythematosus, Behçet disease, Churg-Strauss syndrome, and rheumatoid arthritis. The clinicopathologic features of system vasculitides involving the gastrointestinal tract have recently been reviewed.\textsuperscript{1} Notably, systemic vasculitides presenting as florid gastrointestinal phlebitis are rare and clinically it is unusual for these systemic illnesses to have an isolated colonic manifestation. Histologically, these conditions primarily involve the arteries but not the veins. Similarly, mesenteric vascular lesions may be seen in Crohn disease; however, it is different from ELP as Crohn disease primarily involves the arteries.

**CONCLUSION**

Enterocolic lymphocytic phlebitis is a rare entity of unknown etiology and pathogenesis. It usually runs a benign course with surgical resection being curative. Clinical presentation of ELP varies widely from chronic inflammatory bowel-type picture to acute abdomen or abdominal mass. Furthermore, histologic diagnosis of ELP requires submucosal vessels, which are difficult to obtain with endoscopic biopsies.\textsuperscript{13} Often, biopsies are superficial and may only show features of ischemic colitis. Thus, preoperative diagnosis is often difficult, and diagnostic misinterpretation and mistherapy are common as a venous source of intestinal ischemia is seldom suspected and is overlooked.\textsuperscript{6,12}

Further studies on the pathogenesis and clinicopathologic characteristics of this entity will allow accurate definition of this disease, reduce confusion in terminology, and permit better understanding between pathologists and clinicians.

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**References**