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STRUCTURAL CHANGES OF THE DIAPHRAGMATIC PERITONEUM IN PATIENTS WITH SCHISTOSOMAL HEPATIC FIBROSIS: ITS RELATION TO ASCITES

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ABSTRACT

The histopathologic changes of the peritoneum of the hemidiaphragm were studied in 30 patients with schistosomal liver disease and compared with ten control subjects. The diaphragmatic peritoneum of patients with ascites was markedly thickened with infiltration of inflammatory cells and collagen bundles resembling the interstitial changes of peripheral lymphedema. Obliteration of diaphragmatic lymphatic stomata with restricted lymph flow as well as excess lymph formation from portal hypertension are both major factors in the magnitude and intractability of ascites associated with schistosomal hepatic fibrosis.

The peritoneal cavity is a specialized tissue space, and ascites constitutes a subcompartment of an expanded splanchnic lymph volume (1,2). Ascitic fluid is a continuously circulating medium (3-5), and peritoneal absorption is mainly through the lymphatics of the diaphragm (6-9). Sherlock (10), Summerskill and Baldus (11), have suggested that alterations in peritoneal permeability are among the pathogenetic factors contributing to ascites, and Schreiber et al (12) have suggested that plugging of peritoneal lymph stomata by fibrin-rich lymph in longstanding ascites restricts peritoneal lymphatic absorption.

The present work examines the histopathologic changes of the diaphragmatic peritoneum in patients with schistosomal hepatic fibrosis.

MATERIAL AND METHODS

Thirty schistosomal male patients (age 19 to 50 years) were studied. Ten had schistosomal hepatic fibrosis but none had ascites nor hemorrhage; 10 had variceal hemorrhage and 10 had repeated accumulation of ascitic fluid despite intensive dietary sodium restriction, diuretic drugs and high-vitamin, high-protein diet. The duration of ascites was from three to five years. We also examined ten "control" patients without hepatic disease or portal hypertension. These patients also were males aged 17 to 54 years. None had peritonitis before or at time of operation, previous abdominal operation, neoplastic disease or other processes affecting the peritoneum.

Peritoneal specimens were taken from the left hemidiaphragm during splenectomy and decongestion operations, emergency management of traumatic rupture of the normal spleen, and operation for non-complicated chronic peptic ulcer disease. Patients with dense splenic adhesions were excluded, and wedge liver biopsies for histopathology were taken from all patients

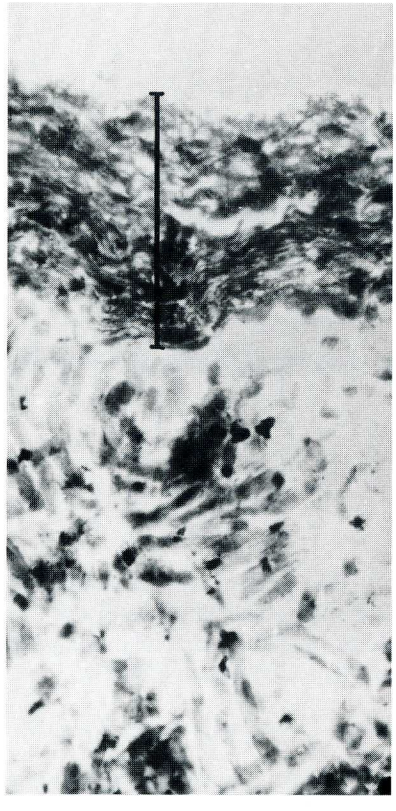

Fig. 1: Normal diaphragmatic peritoneum (x 180).

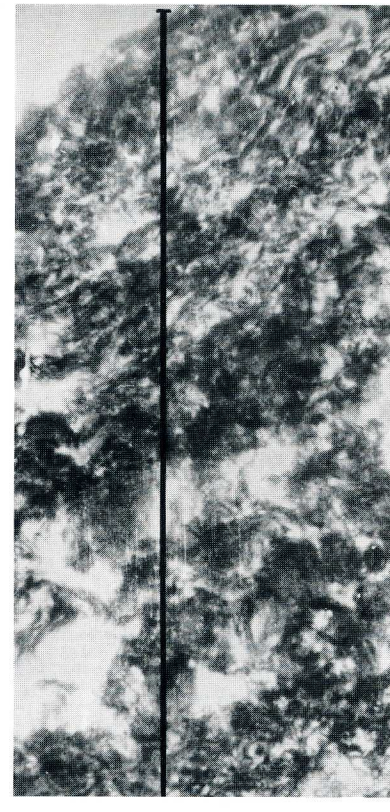

Fig. 2: Increased thickness of diaphragmatic peritoneum of a schistosomal patient with refractory ascites (x 180).

with schistosomiasis. The specimens included the peritoneum and portion of underlying diaphragmatic muscles. Biopsy fragments were fixed in 10% buffered formalin, cross-sectioned perpendicularly, cut at 5 μm thickness, and stained with hematoxylin and eosin, alcian blue and PAS, and Verhoff's Van Geison stains. The peritoneal thickness from the serosal surface to the outer limits of the muscular layer was measured by an ocular micrometer.

Fresh peritoneal samples of five patients from each group (schistosomal and control) were promptly fixed in phosphate-buffered glutaraldehyde, postfixed in Os O_4, dehydrated and embedded in araldite. Ultrathin sections were stained with uranyl-acetate solution (1:1 with acetone as a mixture), for ten minutes, lead citrate solution for 25-30 minutes (13), and studied in a Siemens Elmiscope 101.

The cellular elements, collagen, elastic fibers, vascularity and lymphatic spaces were studied and compared.

Table 1.
Diaphragmatic peritoneal thickness (DPT) in 30 patients with schistosomal hepatic fibrosis and 10 control subjects
(Mean values ± S.E.).

PATIENTS	(n)	DPT (μm)
Controls	10	320.8± 29.8
Schistosomal:		
Non-bleeders	10	460.8± 77.5*
Bleeders	10	737.7±103.8**
Ascitics	10	1475.8±124.8***

*$p > 0.05$; **$p < 0.01$; ***$p < 0.001$

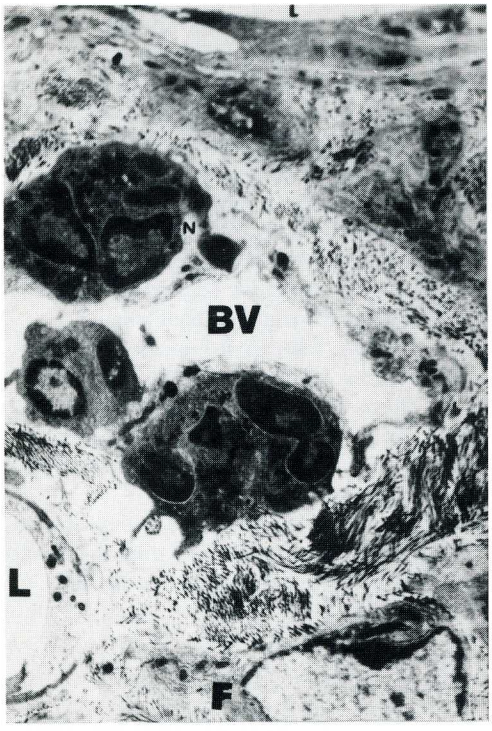

Fig. 3: Diaphragm from ascitic patient showing blood vessel (BV), lymphatics (L), edema, active fibroblast (F), neutrophil (N) and collagen fibers (x 13,000).

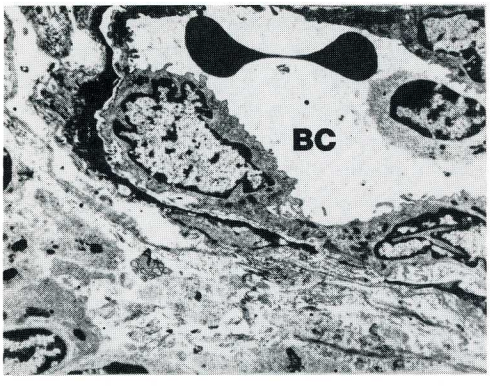

Fig. 4: Ascitic schistosomal specimen showing blood capillary (BC), fibromuscular hyperplasia and small collagen fibers (x 10,000).

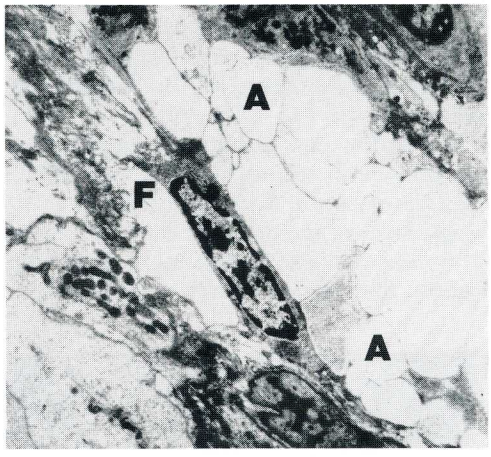

Fig. 5: Ascitic schistosomal specimen depicting fibroblast (F) with filled endoplasmic reticulum and elongated processes. Many adipocyte-like cells (A) also seen (x 10,000).

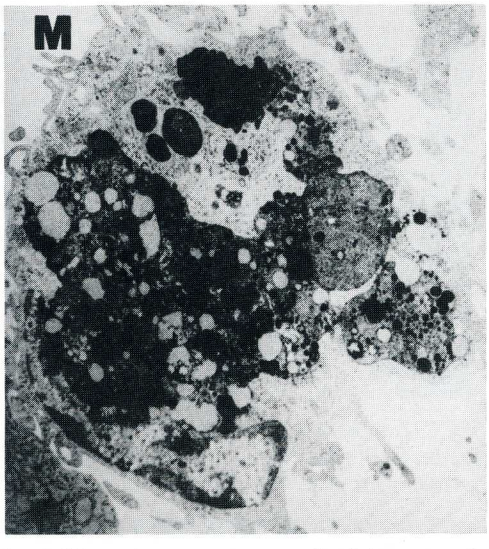

Fig. 6: Macrophage contain many lipid deposits and elongated processes (x 6,000).

RESULTS

Each patient had no other parasitic infestation, and hepatic and renal function were normal. The schistosomal etiology of hepatic fibrosis in the 30 patients studied was established as their being farmers, living in a rural area, having received repeated courses of antischistosomal drugs and the histopathology of the liver biopsy. The latter showed "pure" schistosomal fibrosis in 21 patients (70%) and mixed schistosomal

fibrosis and cirrhosis in the remaining nine patients. In "ascitic" patients, the incidence of "mixed" hepatic changes was 40%, and peritoneal fluid contained total proteins in the range of 1.1 to 2.1 gm/dl.

The thickness of the diaphragmatic peritoneum in control patients was 320.8 ± 29.8 μm (mean ± S.E.). It contained a single layer of mesothelial cells and a layer of fibrous tissue with occasional small blood vessels, fibroblasts, and few a lymphatics.

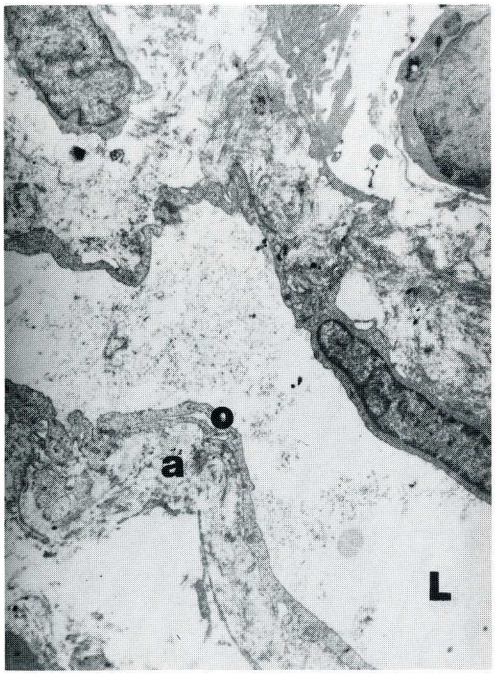

Fig. 7: Lymphatic capillary (L) with anchoring filaments (a), partly open junction (O) and much protein in the lumen (x 7,000).

Significantly increased peritoneal thickness was found in schistosomal patients with variceal hemorrhage and those with intractable ascites (*Table 1, Fig. 1,2*). In these patients, moreover, in the fibrous tissue layer of the diaphragmatic peritoneum, there was a marked increase of blood vascular channels with numerous dilated veins, edema, increased acid mucopolysaccharides, diminished elastic fibers, dense collagen bundles, fibromuscular hyperplasia, cellular proliferation (primarily fibroblasts), macrophages, few small lymphocytes, few granulocytes and adipocyte-like cells (*Fig. 3-6*). There were also dilated lymphatics with a high density of proteins and endothelium with many vacuoles and partly open junctions (*Fig. 7,8*).

The mesothelial layer of the peritoneum of "ascitic" patients showed patent stomata with submesothelial dilated lymphatic lacunae (*Fig. 9*).

DISCUSSION

The present study demonstrates congested diaphragmatic veins in patients with schistosomal hepatic fibrosis and portal hypertension. This congestion is secondary to venous communications between diaphragmatic veins and high pressure left and short gastric veins (14). As lymph arises from plasma by capillary filtration regulated largely by hydrostatic and osmotic pressures on either side of the capillary membrane (15), the sustained rise in diaphragmatic venous and capillary hydrostatic pressure increases filtration of

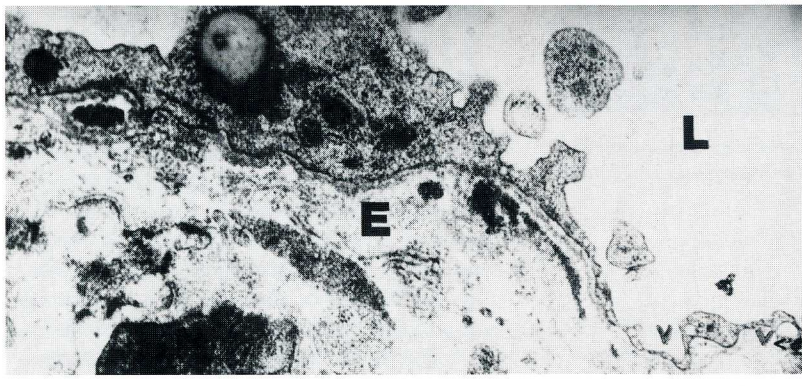

Fig. 8: Endothelial wall (E) of a lymphatic capillary (L) and cytoplasmic process with many vacuoles (V) (x 32,000).

tissue fluid and formation of regional lymph. This surplus lymph ordinarily is drained by central lymphatics which in schistosomiasis are overloaded and inefficient particularly in patients with refractory ascites (1,16,17). Limited lymph flow and excess tissue fluid formation probably account for the marked edema and lymphangiectasia in the diaphragmatic peritoneum.

Although prolonged venous congestion induces non-specific inflammation (18), that may in part explain the presence of inflammatory cells in the fibrous tissue layer of the diaphragmatic peritoneum in patients with schistosomiasis, immune reactivity may also be incriminated, as indirect immunofluorescence also demonstrates diaphragmatic immune complexes of IgG, IgM, and complement fraction C_3 deposits (19).

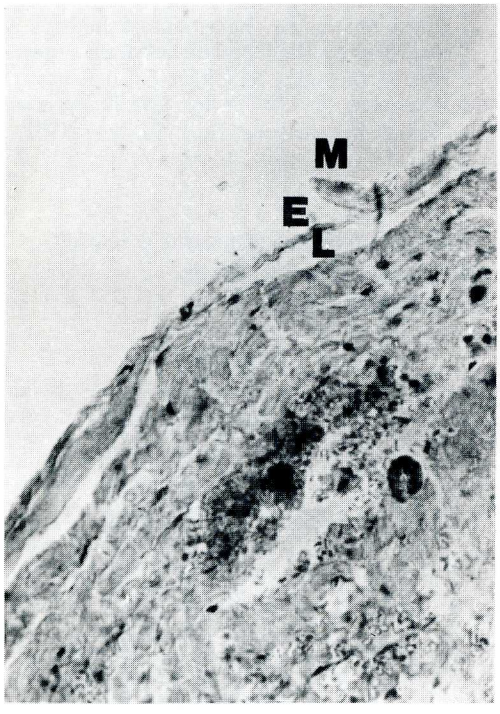

Fig. 9: Diaphragmatic peritoneum of a schistosomal patient with refractory ascites, showing stoma between neighboring mesothelial (M) and endothelial (E) cells. The submesothelial lymphatic lacuna (L) is dilated. Note: blood vessels and mononuclear cell infiltration of the fibrous tissue layer (x 400).

Stagnant edema fluid becomes infiltrated and replaced by fibrosis with loss of tissue elasticity and progressive resistance to compression (20). Increasing bundles of compact collagen in close proximity to lymph and blood vascular channels further restrict the motility and function of overloaded lymph collectors (21), and as protein-rich edema fluid intensifies, the characteristic histopathology associated with chronic lymphedema gradually evolves (22). Comparable changes occur in the diaphragmatic peritoneum of patients with schistosomiasis and refractory ascites, which come to resemble the structural abnormalities of peripheral lymphedema (23).

Because ascitic fluid is in relative equilibrium with central lymphatic drainage capacity, the presence and magnitude of ascites depends to a large extent upon peritoneal absorption and the capacity of diaphragmatic lymphatics and their collateral (compensatory) pathways. Those patients with extensive diaphragmatic scarring and therefore limited peritoneal absorption and/or impaired or restricted drainage of central lymphatics including the thoracic duct are especially prone to develop intractable ascites.

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