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LYMPHOCYTE AND ERYTHROCYTE TURNOVER IN THORACIC DUCT LYMPH IN PATIENTS WITH SCHISTOSOMAL HEPATOSPLENOMEGALY AND PORTAL HYPERTENSION

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ABSTRACT

In 60 patients with hepatosplenic schistosomiasis and portal hypertension and in 20 control subjects, the turnover of erythrocytes and lymphocytes circulating in thoracic duct lymph was compared. Despite slight anemia in most patients with schistosomiasis, there was a greatly accelerated extravascular splanchnic circulation rate of erythrocytes. Lymphocytes also circulated more rapidly, but in contrast to erythrocytes, the peripheral blood lymphocyte count was elevated in schistosomal patients. Although thoracic duct lymph flow was increased at all stages of schistosomiasis, it was less rapid in "ascitic" and "varix bleeders" and thus the extravascular circulation turnover of erythrocytes and lymphocytes appeared to decline with chronicity of disease. The more rapid lymphocyte and erythrocyte "turnover," however, was almost entirely due to increased formation of interstitial fluid (greater lymph flow) suggesting that a prime regulator of splanchnic cellular migration was "solvent drag." These findings may derive from deranged portal microvascular dynamics (e.g., increased microvascular pressure, collagen deposition in Disse's space, capillarization of hepatic sinusoids, presinusoidal obstruction) as well as generalized host immunoresponsiveness to schistosomal infection.

It is now recognized that there is a continuous circulation of peripheral blood elements in both the intravascular and extravascular compartments. Lymphocytes which enter the bloodstream via thoracic duct lymph (the major common extravascular pathway), circulate briefly, and then migrate to peripheral lymphatic tissues including the spleen. Several hours later these cells reenter the bloodstream directly from the spleen or indirectly from lymph nodes and intestinal lymphatic tissue. Thoracic duct lymphocytes are a heterogenous population, with the vast majority (90-95%) composed of small recirculating lymphocytes and a small component of blast cells (5-10%) that do not recirculate. Both T cells and B cells circulate with T cells representing 70% and B cells 20-25% of lymphocytes in the peripheral blood.

During the course of investigation into thoracic duct lymph kinetics, we examined the turnover rate of lymphocytes and erythrocytes in patients with schistosomal hepatosplenomegaly at different clinical pathological stages.

MATERIALS AND METHODS

Sixty patients with schistosomal hepatosplenomegaly and portal hypertension (20 nonbleeders, nonascites, 20 with history of bleeding varices, and 20 with ascites) were studied. Another 20 non-schistosomal patients undergoing operation for simple goiter served as control subjects. Cannulation of the thoracic duct was ex-

Table 1
Thoracic duct lymph erythrocyte and lymphocyte transport

Group No.	*TDLF (ml/min)*	*TDLL (mm^3)*	*TDLE (mm3)*	*TDLE/ TDLL*	*TDLL Transport (counts/mm^3/min)*	*TDLE Transport (counts/mm^3/min)*
Control (20)						
Mean	0.82	7825	176,000	22.3	6.4×10^5	14.2×10^6
SD	0.3	847	31,692	3.8	2.8×10^5	2.3×10^6
Schistosomiasis						
Nonbleeder (20)						
Mean	8.5	9080	103,400	11.0	76.7×10^5	70.9×10^6
SD	1.8	533	29,135	3.6	11.5×10^5	34.6×10^6
Bleeders (20)						
Mean	3.45	7665	87,800	11.3	26.5×10^5	30.9×10^6
SD	0.76	355	22,640	3.5	8.1×10^5	12.3×10^6
Ascites (20)						
Mean	5.4	8100	83,600	9.8	43.5×10^5	44.6×10^6
SD	1.4	266	25,802	3.8	11.3×10^5	14.3×10^6

TDLF = thoracic duct lymph flow; TDLL = thoracic duct lymph lymphocytes; TDLE = thoracic duct lymph erythrocytes

plained to each patient and an informed consent was obtained.

Diagnosis of chronic schistosomiasis with portal hypertension was based on history, clinical findings, and confirmed by liver biopsy and histopathology. Individuals with acute schistosomiasis as demonstrated by living ova in urine or stools were excluded. Other aggravating factors such as malnutrition, vitamin deficiency, and other parasitic infestations were looked for and when present these patients were also excluded. A peripheral blood sample (heparin anticoagulant) was taken just before operation and examined for erythrocyte and lymphocyte count. Throughout peripheral blood counts were done by Coulter Counter and the differential count with Leishman stain.

The thoracic duct was cannulated in the neck and lymph samples were collected and sterile bottles heparinized with 20 IU heparin. The first fasting sample of lymph was tested for the total and differential cellular content of lymphocytes and the total number of erythrocytes. The rate of thoracic duct lymph flow was taken as the mean of ten measurements over a one-minute duration. The lymphocyte and erythrocyte output per minute in lymph was calculated as the product of the lymph concentration and the rate of thoracic duct lymph flow or Cellular output = Cell concentration/mm^3 × TDL (ml/min) × 1000.

RESULTS

The thoracic duct lymph flow in schistosomal patients varied with the clinicopathological stage. In non-bleeder, nonascitic patients ("early" disease) the range was 6-12ml/min (mean 8.5 ± 1.8ml/min); in patients with hematemesis it was 2.5-5.5ml/min (mean 3.45 ± 0.78ml/min) and in "ascitic" patients, it was 4-9 ml/min (mean 5.4 ± 1.4ml/min). Thoracic duct lymph flow showed a significant difference among the schistosomal groups ($p<0.01$). In the control subjects TDL flow was only 0.5-1.5ml/min (mean 0.82 ± 0.3ml/min).

The erythrocyte and lymphocyte turnover in thoracic duct lymph in control subjects and patients with schistosomal hepatosplenomegaly and portal hypertension are shown in *Table 1*. Patients with schistosomiasis showed an increase in both erythrocytes and lymphocytes when compared to normal, but this increase was primarily due to greater lymph flow rate as lymph concentrations were similar to controls. Patients with more advanced schistosomiasis ("bleeders" and "ascites") also showed less turnover than "early" schistosomiasis, but again this difference was related mainly to less rapid lymph flow.

DISCUSSION

The findings demonstrate large volume extracellular splanchnic fluid, lymphocyte and erythrocyte turnover in patients with schistosomal hepatosplenomegaly and portal hypertension. Most of this extravascular turnover is related to accelerated extravasation of fluid into splanchnic tissues with solvent drag "pulling along" peripheral blood elements. Whereas there may be an increased contribution from lymph nodes and the spleen, cellular concentrations in central lymph of erythrocytes and lymphocytes (cellular density) are similar to control values. There is somewhat greater density of lymphocytes in schistosomiasis, but this increase is proportional to peripheral lymphocytosis and probably reflects a generalized immunoresponsiveness to the parasitic infestation.

The pathomechanism of the cellular turnover of erythrocytes and lymphocytes and its overall significance is, however, less clear. Ordinarily lymph is almost free of erythrocytes and platelets. Whereas greater capillary filtration as with increased microvascular pressure increases interstitial fluid extravasation and lymph formation, extravasation of cellular elements is not notably increased unless capillary integrity is compromised (as for example with capillary pressure $>$ 50mmHg). Similarly with diuresis induced by mannitol infusion, fluid extravasation is sharply increased across glomerular capillaries. Whereas this solvent effect "drags along" smaller ions (e.g., Na^+, K^+, Cl^-) larger molecules such as plasma protein and cellular elements are not usually increased in resultant urine. Indeed, their appearance usually signifies a structural alteration in filtering capillaries or adjacent tubules. In this light, the findings in schistosomal portal hypertension of greater "leakage" of lymphocytes and erythrocytes into central lymph suggest alteration in microvascular structure. Because previous studies in analogous syndromes (e.g., portal hypertension from alcoholic and posthepatitic cirrhosis) suggest extrahepatic portal capillaries are structurally intact, it is reasonable to conclude that the liver and specifically the diseased hepatic sinusoid is the likely site of cellular extravasation. Deposition of collagen along the sinusoidal endothelium, in the spaces of Disse or portal perfusion defects (presinusoidal obstruction) may alter capillary dynamics. Similar but more marked changes in hepatic microvascular architecture may account for less prominent findings in "late" (i.e., "bleeders" and "ascites") as compared with "early" (i.e., nonbleeders and nonascites) schistosomal hepatic disease.

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