Development of Hodgkin's disease in the course of liver cirrhosis and impaired monocyte function

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Summary

The monocyte function, as measured by phagocytosis and killing of *Candida albicans* and *Candida pseudotropicalis* by peripheral blood monocytes, was found impaired in a patient with cirrhosis of the liver on two separate determinations before the occurrence of bleeding from oesophageal varices. Unexpectedly, Hodgkin's disease was diagnosed in enlarged abdominal lymph nodes found on the occasion of an emergency portocaval shunt operation.

KEY WORDS: bacterial peritonitis, phagocytosis.

Introduction

The development of a lymphoproliferative disease in association with a chronic liver disease, although uncommon, has been documented in several reports (Heimann, 1971; Viteri, Vernace and Schaffner, 1976; Slavin *et al.*, 1974). It was suggested that this association is possibly not a fortuitous coincidence, but influenced by the prolonged antigenic stimulation as a result of the impaired reticuloendothelial function in the diseased liver (Naparstek and Eliakim, 1979). In contrast to earlier published opinions (Sherlock, 1977) we found distinct decreased monocyte function in this case, as in other cirrhotic patients (Hassner *et al.*, 1979).

Case report

Cirrhosis of the liver was diagnosed in a 57-year-old man in February 1978 following the appearance of ascites and peripheral oedema. There was no history of alcohol abuse, infectious hepatitis or administration of hepatotoxic drugs. The diagnosis of liver cirrhosis was confirmed by liver biopsy. He received diuretic therapy which was continued after discharge.

In December 1978 the patient was admitted to our department with fever and abdominal pains shown to be due to spontaneous *Escherichia coli* peritonitis, which responded to antibiotics therapy. He recovered and was discharged after 21 days with diuretic therapy, and appeared regularly for follow-up.

The patient was readmitted in August 1979 with another episode of chills, high fever and abdominal pains. Abdominocentesis revealed turbid fluid rich in polymorphonuclear cells, and antibiotic therapy was initiated. On the second hospital day bleeding from oesophageal varices occurred, and a Blakemore tube was inserted. Hepatitis B surface antigen (HB_sAg) was absent.

Sixteen days later he had melaena. After demonstration of oesophageal varices on gastroscopy, an end-to-end portocaval shunt was performed. At laparotomy enlarged para-aortic lymph nodes were found. Histological examination of the enlarged lymph nodes revealed Hodgkin's disease, mixed cellularity type. Reed-Sternberg cells were found also in the bone marrow. Because of the poor prognosis due to advanced liver disease, we decided not to treat the lymphoproliferative disease. He succumbed 6 months later from hepatic coma.

At autopsy generalized lymphadenopathy was found, predominantly para-aortic, coeliac and mesenteric. The abdomen contained 250 ml of ascites. The liver was contracted and diffusely nodular, and the spleen weighed 850 g.

Special study

Monocyte activity was evaluated during a clinical study of monocyte function in patients with cirrhosis of the liver.

Monocyte phagocytosis and intracellular killing of

TABLE 1. Peripheral monocyte activity in the present patient compared to a group of cirrhotic patients and normal controls

	Phagocytosis*		Intracellular killing†	
	<i>C. pseudotropicalis</i>	<i>C. albicans</i>	<i>C. pseudotropicalis</i>	<i>C. albicans</i>
This case	1.2 ± 0.02 (<i>P</i> < 0.05)	1.23 ± 0.02 (<i>P</i> < 0.05)	24.6 ± 2.6 (<i>P</i> < 0.0025)	21.8 ± 2.96 (<i>P</i> < 0.0005)
Cirrhotic patients (<i>n</i> = 16)	1.17 ± 0.08 (<i>P</i> < 0.0025)	1.2 ± 0.07 (<i>P</i> < 0.005)	24.99 ± 7.41 (<i>P</i> < 0.0001)	28.22 ± 4.11 (<i>P</i> < 0.0001)
Controls (<i>n</i> = 9)	1.25 ± 0.06	1.33 ± 0.13	40 ± 9.13	44.22 ± 6.17

*Mean of yeast cells per monocyte; †Mean % of killed yeasts. Values are means ± s.d. In parentheses are *P* values comparing results from the present patient and a group of cirrhotic patients to controls. Data about controls and cirrhotic patients obtained with permission (Hassner *et al.*, 1979).

Candida albicans and *Candida pseudotropicalis* was measured using the method of Territo and Cline (1977). The measurements were performed under the same basic conditions in two blood samples at 2-monthly interval, 1 year before the portocaval shunt operation. The results are compared to normal controls matched for age and ethnic origin. Statistical analysis was by Student's *t*-test.

Table 1 gives results obtained from nine normal controls, 16 patients with cirrhosis of the liver and the present case.

We found that phagocytosis and intracellular killing of *Candida* yeasts by peripheral blood monocytes from our patient were statistically significantly reduced compared to a control group, and were in accord with results obtained in a previous study of patients with cirrhosis of the liver (Hassner *et al.*, 1979).

Discussion

The causal relationship between chronic liver disease and lymphoproliferative disease is difficult to prove, and only a large prospective study will answer this question clearly. However, several mechanisms explaining the development of lymphoma in the course of liver disease have been offered: prolonged antigenic stimulation (Prytz *et al.*, 1977), immunosuppressive therapy (Viteri *et al.*, 1976; Harris, 1976) and presence of hepatitis B surface antigen (Wands *et al.*, 1975).

Prolonged antigenic stimulation has been suggested to be operative in chronic liver disease, resulting most probably from the decreased antigenic elimination by the diseased liver with impaired reticuloendothelial function (Prytz *et al.*, 1977). The permanent antigenic stimulation maintains a proliferation of the lymphoid system which could deviate towards malignancy (Editorial, 1970). This mechanism was demonstrated experimentally in animals (Metcalf, 1961), and was offered to explain also the increased frequency of lymphomas in autoimmune disease (Miller, 1967).

The reticuloendothelial system, or more properly designated, the mononuclear phagocyte system, has been widely studied in recent years (Cline, 1978). The activity of Kupffer cells, which belong to this system, has already been partially studied in the diseased liver, and was found impaired (Prytz *et al.*, 1977; Bjorneboe, Prytz and Orskov, 1972). Sherlock (1977) has stated that there were no data available that monocyte function is impaired in cirrhosis of liver, but that these cells are functionally incapacitated by the by-pass of portal blood by way of the portocaval anastomoses. In contrast, recent preliminary publications have reported impaired monocyte function in liver cirrhosis as measured by phagocytosis or killing of *Candida* (Hassner *et al.*, 1979) or by measuring monocyte chemotaxis (Holdstock, Hill and Wright, 1979).

While in the majority of reported cases of the occurrence of lymphomas in chronic liver disease immunosuppressive therapy was given (Viteri *et al.*, 1976; Pirrote, 1974), it is of note that no such treatment was administered in our case. In this context the finding of impaired monocyte function in our patient deserves special attention.

Our findings of impaired monocyte function in patients with liver cirrhosis could point to an additional factor involved in the lowered resistance to infection of these patients. Furthermore, impaired monocyte function would most probably expose these patients to prolonged antigenic stimulation. The patient described in this report demonstrated two possible complications of the decreased immunocompetence in cirrhosis of the liver: the appearance of spontaneous recurrent peritonitis and the development of Hodgkin's disease in the abdominal lymph nodes. It seems that chronic liver disease should be added to the list of conditions with immunological disturbances associated with malignant diseases.

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