Homologous Serum Hepatitis Occurring in Laennec's Cirrhosis

Report of a Case

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IN THE ABSENCE of specific tests for the causative factors in liver disease, any etiologic diagnosis must be based upon circumstantial evidence and microscopy. Homologous serum hepatitis is diagnosed when there is a 40 to 180-day interval between the presumed inoculation of virus and the onset of disease. Microscopic examination of the liver in such cases reveals the predominant lesion to be hepatocellular degeneration and necrosis. Almost all the cells in every lobule are involved in the fulminant form of the disease.

Although necrosis of liver cells is often seen in cirrhosis, it is usually spotty or focal necrosis; rarely, it is limited to one zone of the lobule.[1] A number of factors cause hepatic necrosis in Laennec's cirrhosis, but malnutrition, recent alcoholism, intercurrent infection, anoxemia, and pressure by regenerating nodules are said to be the principal causes. The occurrence of massive necrosis in Laennec's cirrhosis appears to be very rare, judging from the paucity of published reports. There are several reports in the German literature, but most do not permit a definite conclusion about the etiologic factors involved.[2, 3] The present case apparently is unique, in that the microscopic diagnosis of cirrhosis was made more than 60 days before death from homologous serum hepatitis.

CASE REPORT

R.B., No. 71658, a 55-year-old, white, male restaurant operator, was admitted to our hospital on May 7, 1958, for treatment of massive hematemesis. The patient reported that he had consumed moderate amounts of alcohol for at least 30 years; for approximately 5 years be-

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fore admission, there had been a marked increase in alcohol intake, with daily consumption of either whiskey, beer, wine, or all three. The patient's wife stated that his appetite was frequently poor, resulting in a poor dietary intake.

For several weeks before admission, the patient had experienced mild malaise and occasional bouts of nausea and vomiting; some of the vomitus was said to be "black and oily." Also, during the same period, he had noted black stools several times. There was no history of jaundice, acholic stools, dark urine, increase in abdominal circumference, or pedal edema; there was no history suggestive of peptic ulcer.

On the day before admission, the patient began vomiting small amounts of grossly bloody material, culminating in the sudden emesis of approximately "one gallon" of gross blood. He was taken to a local hospital, where his blood pressure was 80/60 mm. Hg. and his hemoglobin was 41 per cent of normal. He was treated with an unknown amount of plasma expander, 500 ml. of whole blood, pressor agents (exact drugs and amount unknown), and intravenous estrogen. The following morning he was transferred to our hospital.

On arrival his blood pressure was 150/80 mm. Hg.; pulse, 100 per minute; temperature, 99.6° F.; and respiration, 16 per minute. He was an obese, middle-aged male of short stature who was acutely ill. The skin and mucous membranes were quite pale. He was slightly apprehensive, but not mentally obtunded. The lungs were clear; cardiac examination was not remarkable, except for a soft, blowing, Grade I-II, apical, systolic murmur. With the patient in the supine position, the abdomen was protuberant, but there was no evidence of ascites. The liver edge was felt approximately 7.0 cm. below the right costal margin. The edge was slightly tender and quite firm, but not nodular; the spleen was not felt. The testes were much smaller and softer than those of the average adult male, but there was no gynecomastia. There were no spider angiomata, the pectoral muscles did not appear atrophic, and there was no palmar erythema. There was no apparent jaundice of the skin or mucous membranes and no dependent edema.

Initial laboratory studies revealed: hemoglobin, 6.4 Gm./100 ml.; hematocrit, 20 per cent; white blood count, 7600/cu. mm. with a normal differential count; bromsulphalein retention, 33 per cent in 45 minutes; blood urea nitrogen, 18 mg. per cent; prothrombin time, 14 seconds, compared with a normal control of 13 seconds; urinalysis, including screening test for bile, negative; serologic test for syphilis, negative.

Subsequently, serial liver function studies were obtained (Table 1).

The presumptive diagnosis was that of bleeding from esophageal varices associated with Laennec's cirrhosis. Since there was no evidence of active hemorrhage at the time of admission, esophageal tamponade

TABLE 1. *Summary of Liver Function Studies*

Date	BSP retention in 45 min.	Bilirubin (mg. %)	Total protein	Albumin	Globulin	Prothrombin (100% = 13 sec.)	Thymol turbidity	Cephalin flocculation
5/ 7/58	33	1.4	6.2	3.7	2.5	14 sec.	5.1	0 -1+
5/16/58	27	1.0					3.7	1+-2+
6/13/58	29		7.1	2.9	4.2	17 sec.		
7/10/58	30	1.2	7.5	3.8	3.7	15 sec.		
7/23/58	25		6.9	3.5	3.4			
7/28/58		1.4				16.5 sec.		
8/15/58	47	1.7	6.9	3.6	3.3	17.5 sec.		
8/25/58		15.0	6.7	2.7	4.0	28 sec.		
8/27/58		26.2						

was not considered necessary, and treatment consisted of sedation, oral antacids, and whole blood transfusion. He received 1500 ml. of whole blood during the first 12 hours, following which his hemoglobin was 8.0 Gm./100 ml. and hematocrit, 26 per cent. On the morning of the second hospital day, x-ray studies were performed; the fluoroscopist noted mucosal irregularity and marked irritability of the distal esophagus, but varices could not be delineated; there was a small hiatus hernia, and both stomach and duodenum were said to be normal otherwise.

Three additional units of whole blood were given during the second and third hospital days, making a total of 3000 ml. During this period, vital signs remained stable and there was no emesis; stool specimens gave a positive test for occult blood until the fourteenth hospital day, after which they were consistently negative.

For the first 6 hospital days, the patient was extremely drowsy and lethargic and on several occasions seemed disoriented and had brief visual hallucinations. The etiology of these phenomena was not clear, but in retrospect they may have been partially drug-induced, since he became alert following the cessation of barbiturate administration.

After the seventh day, the patient improved rapidly and steadily. His appetite returned, his liver edge receded 2-3 cm., and by the fifteenth hospital day his hemoglobin was 11.7 Gm./100 ml. and his hematocrit, 37 per cent. He was given a high-protein, high-carbohydrate diet with vitamin supplements; antacids were continued. Liver function studies showed slight change (Table 1). By the twenty-second day, he was no longer confined to bed.

The gastrointestinal x rays were repeated, but nothing abnormal was noted except a small hiatal hernia. Esophagoscopy revealed definite varices 38 cm. from the incisor teeth. The liver was biopsied with a Vim-Silverman needle; the microscopic report is noted below. Several

consultants agreed that the patient should have a portacaval shunt; therefore, on July 17, 1958, the seventy-second hospital day, he was transferred to the surgical service for further observation in preparation for elective surgery.

Further efforts were made to improve liver function; methionine, inositol, and ferrous sulfate were added to his regimen. On July 25, 1958, bromsulphalein retention was 25 per cent in 45 minutes, and serum total bilirubin was 1.4 mg./100 ml. On July 30, 1958, the patient was granted 2 weeks' leave of absence; he was instructed carefully in the proper diet and advised to abstain from all alcoholic beverages. He returned in apparently good condition, and members of his family corroborated his statement that he had consumed no alcohol. Liver function studies on August 15, however, showed that bromsulphalein retention had risen to 47 per cent and prothrombin time to 17.5 seconds (approximately 50 per cent of normal). The patient showed slight jaundice on August 24; this was 110 days following the original transfusion of whole blood.

His condition deteriorated gradually, and then more rapidly. On August 25, 1958, the serum total bilirubin had risen to 15 mg./100 ml., and 2 days later he was disoriented and uncooperative; the serum total bilirubin now was 26.2 mg./100 ml. During the succeeding 48 hours, he became progressively more drowsy, and on August 27, 1958, he was comatose. The patient was deeply icteric, vital signs were normal, but there was no evidence of recurrent bleeding.

Because of his rapid deterioration, the diagnosis of superimposed viral hepatitis was considered. On August 28, 1958, intravenous hydrocortisone, 300 mg. daily, was begun. He also received 50 Gm. of L-arginine intravenously, but no improvement was noted. On August 30, 1958, his temperature rose to 104° F.; and on August 31, 1958, the one hundred and seventeenth hospital day, he died.

Description of the Liver Biopsy

There was an alteration of the liver architecture manifested by subdivision of the parenchyma into small compartments of uniform size, separated from each other by connective tissue bands of varying widths. There were no identifiable central veins. The portal areas were continuous with these connective tissue bands, and there was some proliferation of bile ducts. Small numbers of lymphocytes were present in the portal areas.

Hepatocellular degeneration was minimal; only a rare parenchymal cell contained a fat vacuole. For the most part, the cytoplasm and nuclei of the cells showed no significant changes (Fig. 1). The argyrophilic

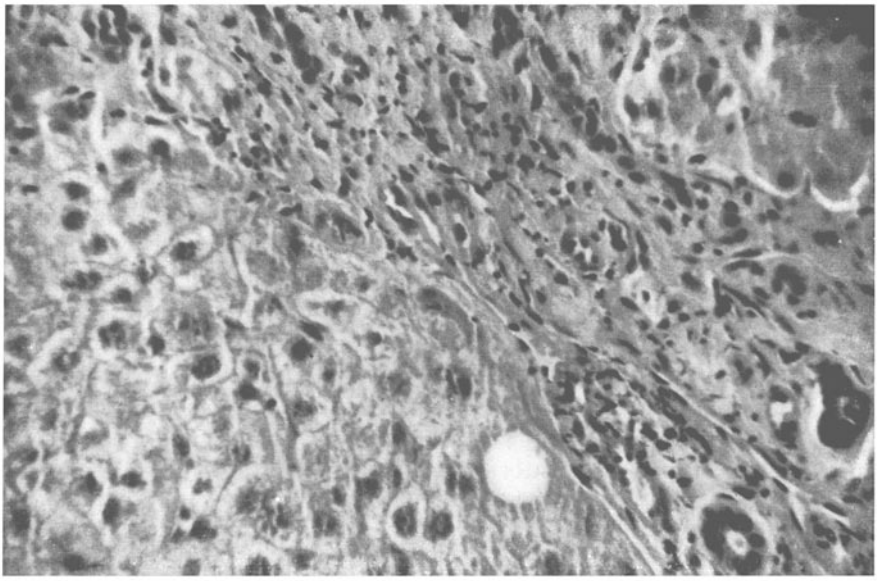


Fig. 1. **Needle aspiration biopsy of liver. There is fibrosis of the portal area which divides the liver into sharply demarcated nodules. Bile duct proliferation and lymphocytic infiltration are present. The parenchymal cells do not show any significant changes (hematoxylin and eosin, × 537).**

reticulum was intact, and there was no evidence of collapsed stroma. The microscopic diagnosis was portal cirrhosis.

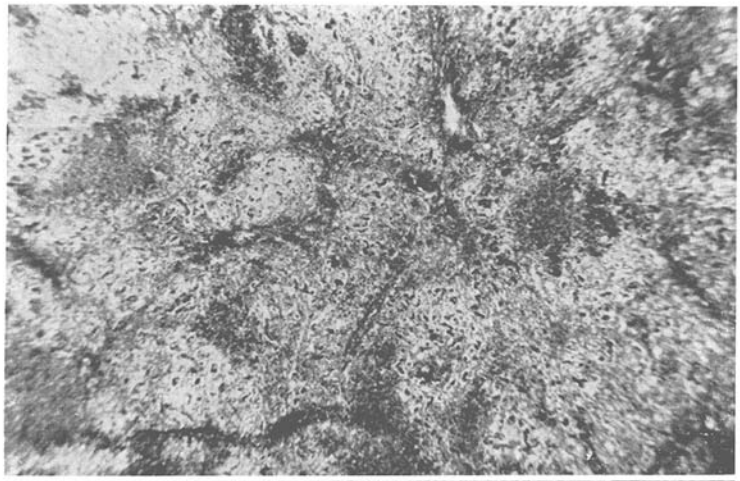
Postmortem Examination

Gross Findings

The body was that of an obese, white male with marked jaundice of the sclerae and skin. There were some scattered petechiae over the back and buttocks. Axillary and chest hair were sparse. There was 500 ml. of yellow fluid in the peritoneal space. The spleen weighed 400 gm. and was soft; the pulp was dark red and diffluent.

The liver weighed 1540 gm. The external surface was brownish-yellow, its edges were rounded, and it was uniformly and finely granular.

Fig. 2. **Section of postmortem liver. The architectural pattern is altered by bands of dense connective tissue, which produces a micronodular lobulation (Masson trichrome, × 44).** ***Fig. 3.*** **Section of postmortem liver illustrating diffuse necrosis of parenchymal cells. Fibrosis is obscured (hematoxylin and eosin, × 125).** ***Fig. 4.*** **Section of postmortem liver. Diffuse necrosis of parenchymal cells (hematoxylin and eosin, × 537).**



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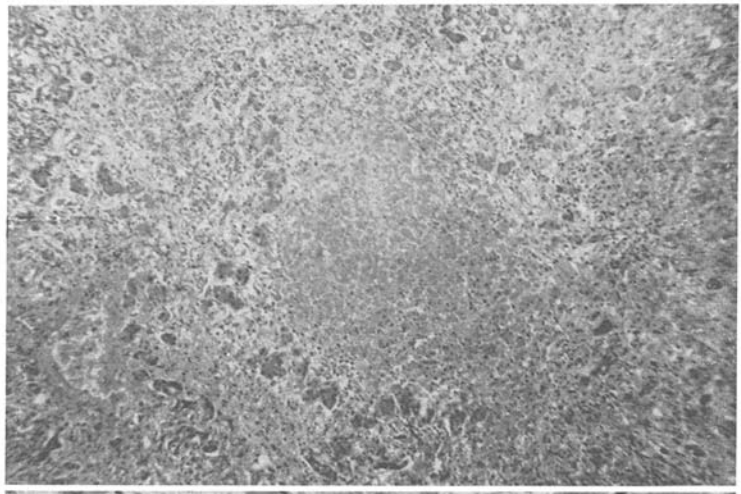

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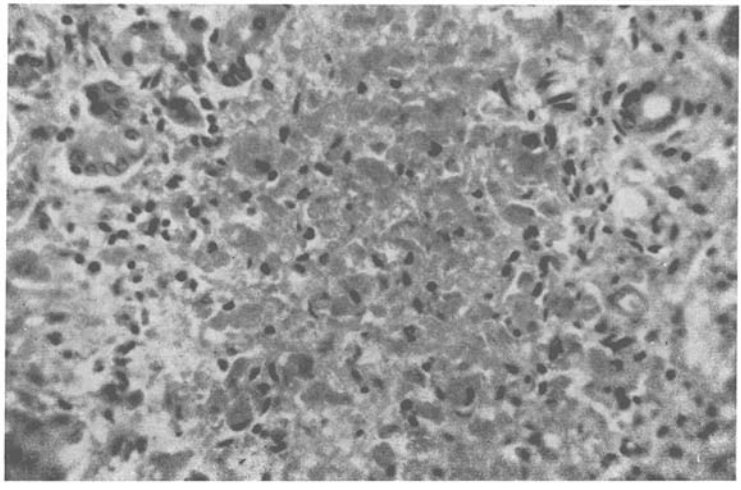

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The right lobe was disproportionately enlarged in comparison with the left. On section, the liver cut with considerable resistance; friability was diminished. The cut surface was reddish-brown and was uniformly and finely granular. The usual architectural markings were obliterated.

There were no abnormalities of the gallbladder, the extrinsic biliary tree, or the extrinsic portal circulation.

The esophagus contained several collapsed dilated veins at its lower end, without a demonstrable bleeding point. The remainder of the esophageal mucosa contained numerous petechial hemorrhages. The stomach was dilated and contained a moderate amount of dark red bloody fluid. Smaller amounts of similar fluid were present in the remainder of the intestinal tract. There were also scattered petechiae in the mucosa of the intestinal tract.

Microscopic Findings

Sections of the liver disclosed the same architectural cirrhotic changes found by needle biopsy (Fig. 2). The striking difference consisted of changes in the parenchymal cells. Almost all the liver cells were completely necrotic (Figs. 3 and 4). At the edges of the nodules, there were infiltrations of lymphocytes, monocytes, and occasional neutrophiles with small zones of hemorrhage. There were a few remaining recognizable parenchymal cells at the periphery of some of the nodules; however, these had undergone hepatocellular degeneration. The portal areas contained increased numbers of lymphocytes and mononuclear cells, and there was bile duct proliferation. Argyrophilic reticulum was intact, although there was some collapse in areas of parenchymal necrosis (Fig. 5).

Collecting tubules in the kidneys contained dark brown casts and monorefringent crystals. The testes revealed marked hyalinization of the tubules; occasional areas showed residual spermatogenesis.

The pathologic diagnoses were: portal cirrhosis, homologous serum hepatitis, splenomegaly, acute splenitis, esophageal varices, acute esophagitis, confluent lobular pneumonia, ascites, and testicular atrophy.

Discussion

The diagnosis of Laennec's cirrhosis was documented by needle biopsy 2 months before death. The etiology of this patient's disease was classic: excessive alcoholic intake and a poor diet. Unusual, however, was obesity and the lack of fatty infiltration of the liver. Since the needle biopsy was obtained on the forty-eighth hospital day, it is possible that some improvement had occurred during the time he received a good diet.

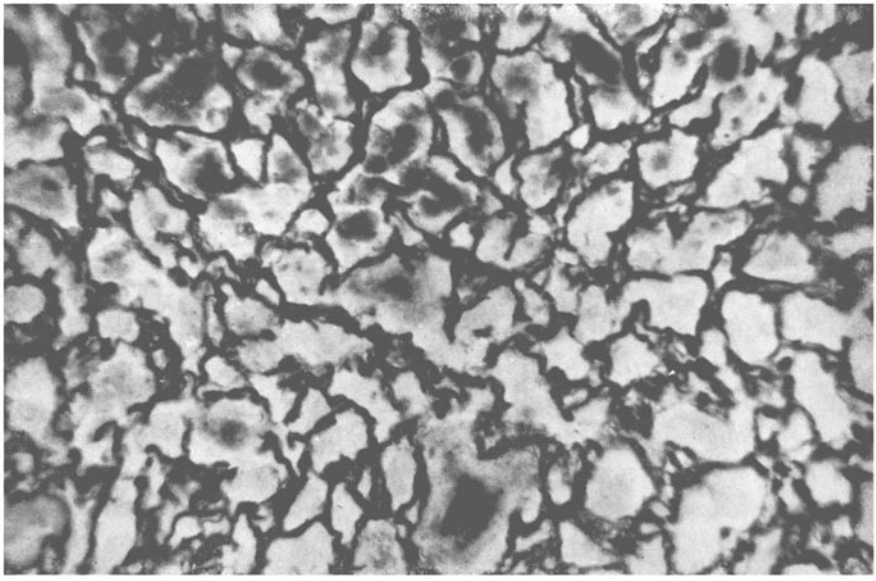

Fig. 5. **Section of postmortem liver. Intact argyrophilic reticulum in area of necrotic parenchyma. Foot's modification of Maresh Bielschowsky silver reticulum (× 537).**

Most important, however, was the absence of hepatocellular necrosis in the needle biopsy specimen. We cannot be certain, of course, but it may have been the morphologic and functional integrity of the liver cells in this patient which permitted the entrance of viral particles at the time of blood transfusion.

One may indeed ask why this does not occur more often in cirrhosis. In recent reports the attack rate of homologous serum hepatitis has been estimated at less than 1 per cent.[4] In our experience, the incidence of serum hepatitis following blood transfusion approximates this figure. It is not unusual to find patients with Hodgkin's disease or aplastic anemia who develop serum hepatitis. Such patients constitute a roughly comparable group of chronically ill patients who require multiple transfusions; why, then, do cirrhotic patients escape serum hepatitis? Again, we cannot answer the question, but we feel that perhaps the virus cannot survive except in relatively normal liver cells. More careful scrutiny of the pathologic material in other hospitals may reveal similar cases of portal cirrhosis in which viral hepatitis developed following blood transfusion.

SUMMARY

A known alcoholic with Laennec's cirrhosis (micronodular, portal, or septal) was awaiting elective portacaval shunt. During this period, he was observed to abstain from alcohol and maintain a good diet. Approximately 4 months after several transfusions of whole blood, he developed severe jaundice and died in hepatic coma 7 days thereafter.

Postmortem examination confirmed the diagnosis of portal cirrhosis and demonstrated acute massive necrosis of the liver with very few intact hepatic cells. Massive necrosis has not been reported in the natural history of Laennec's cirrhosis; hence, in this patient it must have been due to an added toxic or infectious agent. The most likely cause of massive necrosis in this case is the agent responsible for homologous serum hepatitis (Virus B). The coexistence of Laennec's cirrhosis and homologous serum hepatitis is not reported often and even more rarely has it been documented by strict histopathologic criteria for these entities.

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