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Abstract

Three patients at various stages of remission from leukemia died following the development of massive liver necrosis within only 4-6 days. All had either hepatitis B surface antigen or antibody in their sera, and two of them experienced severe epigastric pain before the onset of liver injury. Hepatitis B surface antigen appeared in two of these patients after remission from leukemia. Serum gamma-globulin levels increased with decreasing doses of prednisolone and other antileukemic drugs, and hepatic cell necrosis occurred extensively. Localization of hepatitis B surface antigen in their livers revealed a strong positive reaction in the phagocytic cells. These observations strongly suggest that hepatitis B virus may be causally related to the fulminant hepatic failure at least in two of the reported leukemic patients.

KEYWORDS: fulminant hepatic failure, leukemia, hepatitis B surface antigen, massive liver necrosis, immunosuppressive agents

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FULMINANT HEPATIC FAILURE DURING REMISSION FROM LEUKEMIA: THREE CASES ASSOCIATED WITH MASSIVE LIVER CELL NECROSIS AND HEPATITIS B VIRUS

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Abstract. Three patients at various stages of remission from leukemia died following the development of massive liver necrosis within only 4–6 days. All had either hepatitis B surface antigen or antibody in their sera, and two of them experienced severe epigastric pain before the onset of liver injury. Hepatitis B surface antigen appeared in two of these patients after remission from leukemia. Serum γ-globulin levels increased with decreasing doses of prednisolone and other antileukemic drugs, and hepatic cell necrosis occurred extensively. Localization of hepatitis B surface antigen in their livers revealed a strong positive reaction in the phagocytic cells. These observations strongly suggest that hepatitis B virus may be causally related to the fulminant hepatic failure at least in two of the reported leukemic patients.

Key words: fulminant hepatic failure, leukemia, hepatitis B surface antigen, massive liver necrosis, immunosuppressive agents

It is well established that hepatitis B surface antigen (HBsAg) occurs at a high frequency in patients with leukemia and other hematological diseases associated with frequent blood transfusion and impairment of immunological mechanisms (1). However, the incidence of clinical hepatitis or fulminant hepatic failure in patients with various types of leukemia is unexpectedly rare, and conversely fatal hepatic failure as causes of death in leukemia is again relatively rare (2, 3). Since the antitumor agents impair host defence mechanisms by inhibiting antibody responses and by abolishing the development of delayed hypersensitivity (4), intense therapy with steroids, antibiotics and antitumor agents may be causally related to the clinical manifestations and course of hepatitis associated with hepatitis virus, Type B. We report here on three patients who developed massive liver cell necrosis which resulted in death within only 4–6 days. Two cases had similar severe epigastric pain before the onset of liver injury, and all had either HBsAg or HBs antibody (HBsAb) in their sera.

CASE REPORT

Case 1. A 36-year-old man had frequent attacks of abdominal pain due to cholelithiasis from 1954 to 1965. Many gall stones in intrahepatic bile ducts were removed during the 3rd operation in 1965. The patient was diagnosed as having chronic myeloid leukemia and liver cirrhosis with postnecrotic features in August 1969. He noted tarry stools in November 1971 and was immediately admitted to Okayama University Hospital. Because of deterioration of chronic myeloid leukemia, he received 7 liters fresh blood transfusions and busulfan at a dose of 1 to 4 mg/day. Thereafter, he had persistent HBsAb but never HBsAg. Hematological and clinical improvements were observed. Liver function tests

TABLE 1. SUMMARY OF 3 PATIENTS ASSOCIATED WITH MASSIVE LIVER CELL NECROSIS DURING REMISSION FROM LEUKEMIA

	Case 1	Case 2	Case 3
Days from the onset of the present illness to death	4	6	5
Diagnosis	Chronic myeloid leukemia Cirrhosis of the liver	Acute lymphocytic leukemia	Acute lymphocytic leukemia
Medication received during the last 6 months	Busulfan 0.2 mg/day	Prednisolone 10-80 mg/day Vincristine 1.5 mg/week 6-Mercaptopurine 75-100 mg/day	Prednisolone 20-40 mg/day Vincristine 1.5 mg/week OK-432 0.2-0.5 KE/day Daunomycin 30 mg/day Neocarzinostatin 2 mg/day Cytarabine 60 mg/day
Fresh blood transfusion (the last 6 months)	None	1.8 l	1.2 l
Past history of blood transfusion	11.8 l	None	Large quantities
HBsAg/HBsAb	−/+	+/−	+/−
Initial symptoms of the present illness	Severe upper abdominal pain with fever	Severe upper abdominal pain with fever	High fever
Serum AFP (ng/ml)	2.5	145	46
Microscopical findings of liver and other organs	Massive hepatic necrosis Congestive spleen	Massive hepatic necrosis Retroperitoneal bleeding A stage of remission from acute leukemia	Massive hepatic necrosis

were abnormal but remained constant, showing no acute attack of clinical hepatic failure. Busulfan dosage was decreased from 0.5 to 0.2 mg daily in October 1972. From December 1971 through May 1974, the patient remained very well. He achieved complete hematological remission and was subsequently maintained satisfactorily on extremely small doses of busulfan (Fig. 1).

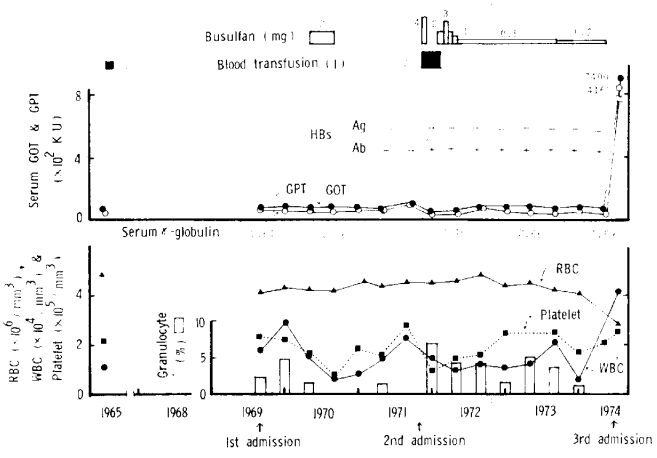


Fig. 1. Clinical course of Case 1.

He complained of the abrupt onset of severe pain in the epigastrium and the right upper quadrant of the abdomen and high fever with shaking chills on May 18, 1974. The next day he had minimal jaundice, vomiting and hematoemesis. He was admitted to a country hospital and received fresh blood transfusions. He became drowsy in the evening and was transferred to Okayama University Hospital on May 20. The liver function tests and other laboratory data on May 21 showed; serum bilirubin 11.4 (direct 8.0) mg/dl, serum GOT 7,400 K. U. (GOTm 27% of total GOT activity), GPT 4,160 K. U., prothrombin time 23 seconds, blood ammonia 614 μg/dl, alkaline phosphatase 3.7 B. L. U., serum amylase 68 Somogyi U., plasma fibrinogen 17 mg/dl, and fibrin-degradation products (FDP) 2 μg/ml. The serum amino acid pattern revealed an aminogram characteristic of patients with fulminant hepatitis rather than of patients with cirrhosis of the liver (5) (Fig. 2). The peripheral blood contained 38,700 white blood cells per cmm, of which 80% were polymorphonuclear cells but no younger cells. The platelet count was 24.8×10^4/cmm. The bone marrow revealed complete hematological remission of leukemia. In May 22, he deteriorated rapidly with the development of marked jaundice, upper gastrointestinal bleeding and irreversible hepatic coma. Despite all therapeutic endeavors, he died 4 days after the onset of illness.

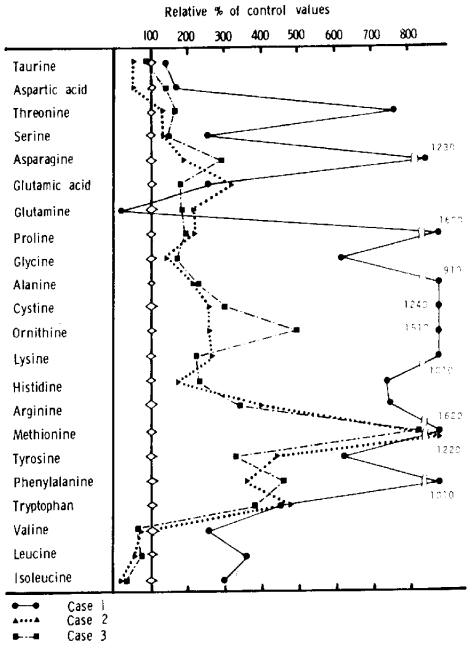


Fig. 2. Serum amino acid pattern in Cases 1, 2 and 3. Amino acid analyses were performed by the previously reported procedure (5). Serum levels of amino acids are represented as relative % of control values from 5 healthy subjects. Diamond-shaped marks indicate standard error of the mean from control subjects.

Liver and spleen necropsy were performed 1 h after death. Microscopically the liver tissue was severely damaged; liver cell necrosis was very extensive and surviving liver cells of the peripheral area were observed only in some remaining micronodules. The nature of necrosis at the central and mid-zonal areas was ischemic. Accumulation of lymphocytes and histiocytes was found in some portal spaces. Myeloid cells were not present. Localization of HBsAg in the autopsied liver was studied with Orcein stain, but no positive reaction was found (Fig. 3). GOTs, GOTm and GPT activities in the liver were found to be 6,500, 9,660 and 11,340 K. U./g liver, respectively, all of which are very low values.

Case 2. A 13-year-old boy had always enjoyed excellent health. In October 1974 the patient noticed a painless lymphonodus enlargement in his neck, and was admitted to the University Hospital for further evaluation. His hemoglobin was 12.5 g/dl, total white cell count 5,200/cmm (premyelocyte 1, polymorphonuclear leukocyte 6, lymphocyte 74, lymphoblast 16, monocyte 1 and erythroblast 2%). The platelet count was 4.4×10^4/cmm. A diagnosis of acute lymphocytic leukemia was confirmed by sternal marrow biopsy. Treatment

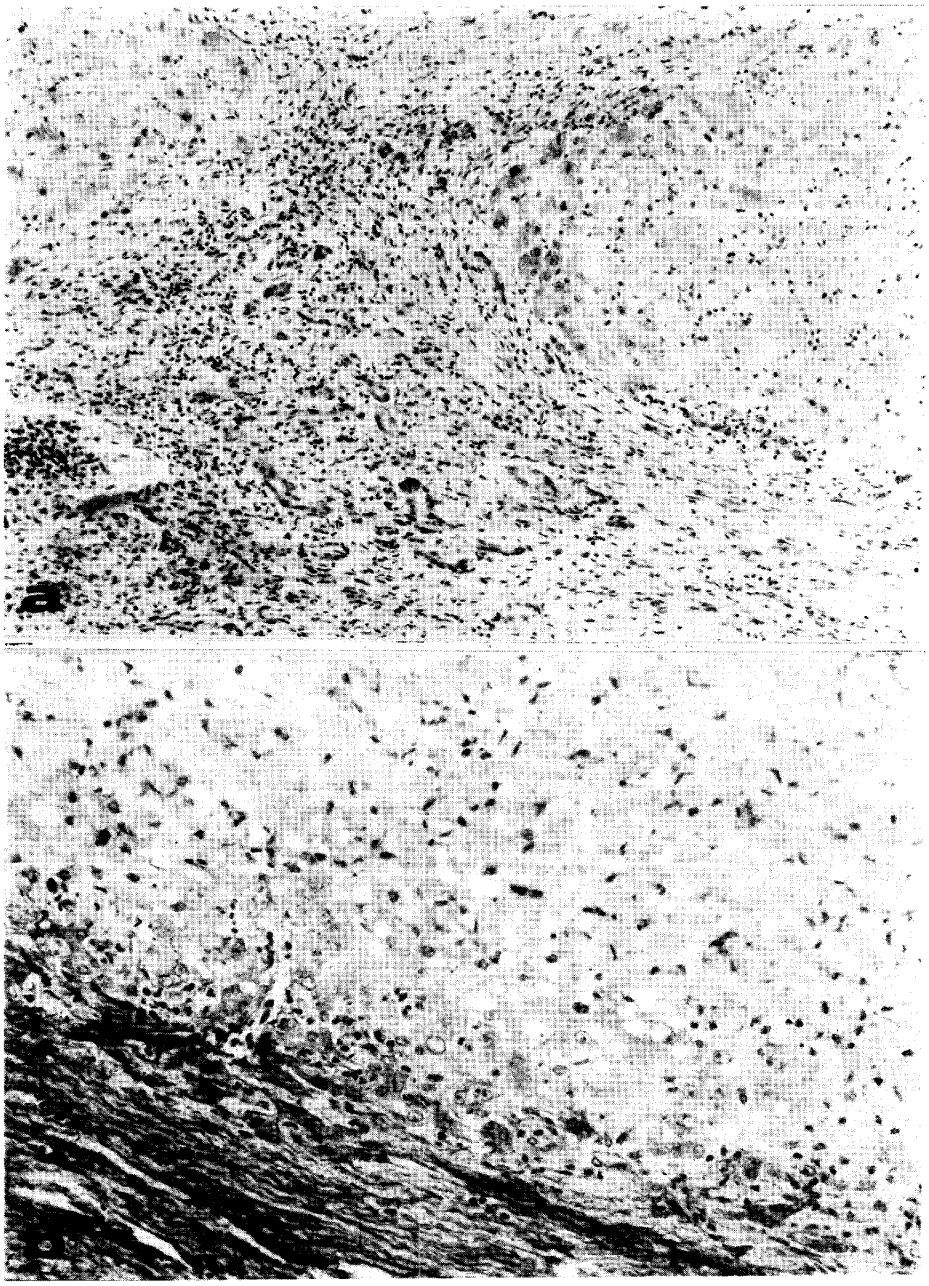


Fig. 3. Liver specimen of Case 1 with chronic myelocytic leukemia, cirrhosis of the liver and acute liver insufficiency. a. Massive necrosis is present with small groups of hepatic cells imbedded in an inflamed and collapsed stroma of reticulin fibers. H-E stain, ×33. b. No positive reaction in liver cells. Orcein stain, ×66.

was started with steroids (40–80 mg/day) followed by vincristine at 1.5 mg/week and later 6-mercaptopurine (6-MP) (100 mg/day) on December 25. Fresh blood transfusions (1.4 l) and antibiotics were given as indicated in Fig. 4. Ten weeks after admission complete remission was obtained as judged by peripheral blood and bone marrow smears and the dose of corticosteroids was decreased gradually.

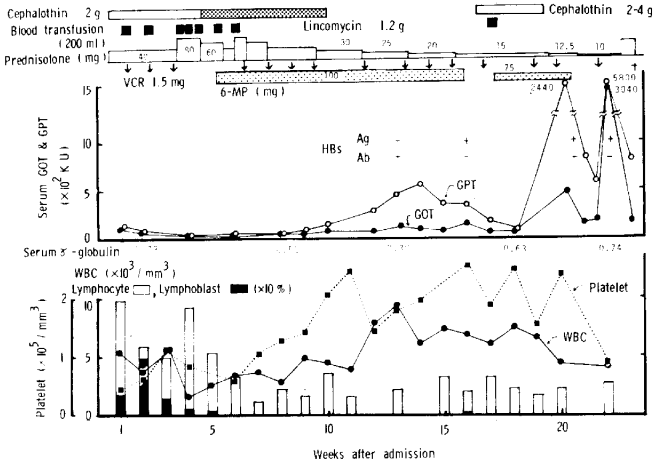
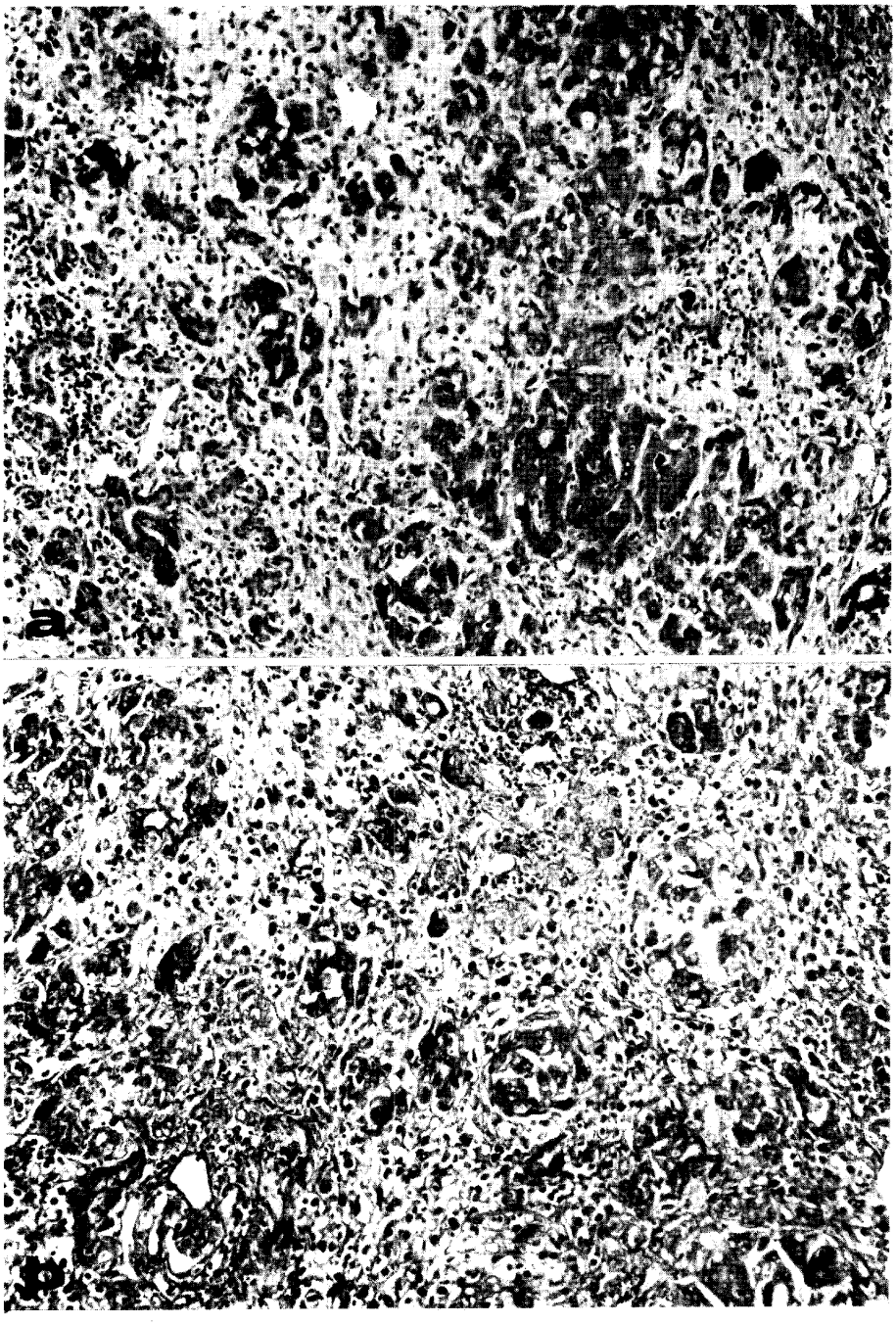


Fig. 4. Clinical course of Case 2.

On February 13 (13 weeks after admission), serum transaminases began to rise. Liver function tests on February 27 showed; serum bilirubin 1.3 (direct 0.4) mg/dl, serum GOT 90 K. U., GPT 550 K. U., and alkaline phosphatase 1.8 B. L. U. He was negative for HBsAg. 6-MP was discontinued on March 15, because 6-MP has been frequently reported to be hepatotoxic (6). The levels of serum transaminases started to decrease gradually to the normal level even before discontinuation of 6-MP. On March 17, HBsAg in his serum was first detected by electrophoresis. Nine days later, 6-MP was reintroduced at a dose of 75 mg daily, although he was already in a stage of remission from acute leukemia. Minimal jaundice was evident on April 11, the 19th day of 6-MP readministration. Liver function tests on April 14 showed; serum bilirubin 4.7 (direct 3.0) mg/dl, serum GPT 2,440 K. U., GOT 430 K. U., and alkaline phosphatase 4.6 B. L. U. 6-MP was immediately discontinued because he had become

Fig. 5. Liver specimen of Case 2 with acute lymphocytic leukemia and fulminant hepatic failure. a. Small groups of liver cells remained in the periportal zone. They contained bile thrombi. Abnormal ductules proliferated considerably. Lymphocytic and plasma cell infiltration and histiocytes were found in the portal space but the lymphoblast was absent. H-E stain, ×100. b. Phagocytic cells mainly in the necrotic areas stained positive with Orcein stain but cytoplasmic stain of liver cells was weak. Orcein stain, ×100.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obviously jaundiced. Liver function tests on April 21 showed; serum bilirubin 0.7 (direct 0.4) mg/dl, serum GPT 600 K. U., GOT 172 K. U., and alkaline phosphatase 3.1 B. L. U. Plasma fibrinogen and FDP concentrations were within the normal limits. On April 25 he began to complain of severe epigastric pain and high fever and the reappearance of marked jaundice was observed. Serum transaminase activities were markedly increased on April 26 (GOT 3,040 and GPT 5,800 K. U.). On April 29 blood ammonia rose to 396 μg/dl and he lapsed into coma. His electroencephalogram showed 2–3 c/s of basic activities (Grade E) (7). He died in the following morning 6 days after the onset of the present illness.

A postmortem examination was performed. The liver weighed 570 g. Macroscopical findings were acute yellow atrophy with fatty infiltration. There were multiple erosions and petechial mucosal bleeding of the upper digestive tract and retroperitoneum. Microscopically the liver tissue had massive hepatic necrosis with slight regeneration of liver cells. The bone marrow showed a stage of remission from acute lymphocytic leukemia. Localization of HBsAg in Orcein-stained liver showed a positive reaction in the phagocytic cells and weak cytoplasmic stain in the liver cells (Fig. 5). The spleen was severly congested.

Case 3. A 16-year-old boy was suspected, judging from his myelogram, of having a relapse of acute lymphocytic leukemia and admitted to Okayama University Hospital for further evaluation in August 1977. He had already been diagnosed as having acute lymphocytic leukemia in November 1973. Administrations of prednisolone, 6-MP, methotrexate and other antileukemic agents resulted in obtaining a stage of remission from acute leukemia. The patient suffered from leukemic meningitis in July 1975, and elevations of serum transaminase activities were temporalily observed at that time. He was admitted 8 times to Hospital because of frequent leukemic relapse, and frequently received various chemotherapeutic agents and large quantities of fresh blood transfusions and leukocyte-rich plasma during these periods. Physical examination on his admission revealed a moon-face. Examination of both sides of the neck revealed 4 small painless lymphonodi. His liver was palpable and accompanied with minimum tenderness, but there was no splenomegaly. Serum bilirubin was 1.2 (direct 0.7) mg/dl, serum GOT 86 K. U., GPT 236 K. U., and alkaline phosphatase 2.6 B. L. U. The peripheral blood contained 2,500 white cells/cmm of which 10% were lymphocytic cells and 5% lymphoblast. The platelet count was 4.7×10^4/cmm.

The patient received prednisolone and OK-432. Elevated activities of serum GOT reached values of 24 on the 22nd day after admission and lymphoblasts in bone marrow decreased significantly to 13.2% 40 days after admission. He also received combined chemotherapy including cytarabine, daunomycin and

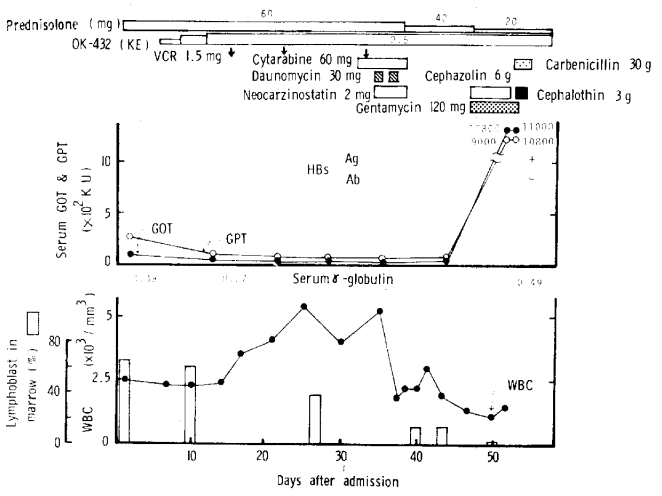


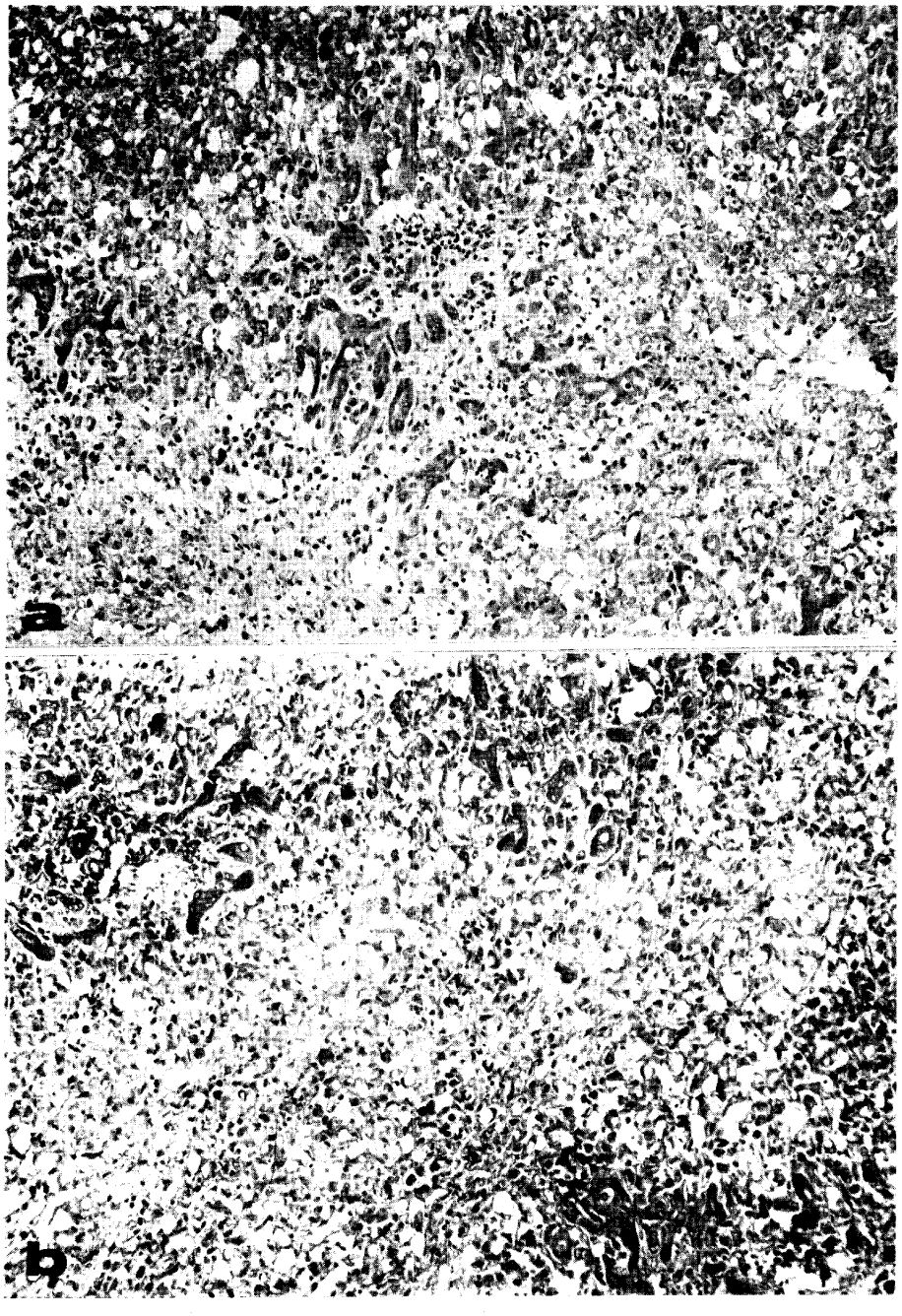
Fig. 6. Clinical course of Case 3.

neocarzinostatin during this period. From the 47th day of admission, he was suspected of having sepsis because of high fever. Antibiotics such as cephazolin, gentamycin and carbenicillin were administered. Marked elevations of serum GOT and GPT were observed with the enlarged liver in the 52nd day. Laboratory data on October 14 showed: serum bilirubin 6.6 (direct 5.3) mg/dl, GOT 10,800 K. U., GPT 9,000 K. U, alkaline phosphatase 4.1 B. L. U., serum amino acid-N 11.7 mg/dl, fibrinogen 200 mg/dl, prothrombin time 39 seconds, and FDP 10 μg/ml. Tarry stool appeared on the morning of the next day, and he lapsed into irritable and excited stages of hepatic encephalopathy. The size of liver dulness was markedly decreased at that time. He deteriorated rapidly with the development of marked jaundice, upper gastrointestinal bleeding and irreversible hepatic coma. He died on the 56th day after admission (Fig. 6).

Liver necropsy was performed 1 h after death. Liver cell necrosis was very extensive and complete loss of the hepatic cords was observed. Deposits of HBsAg were frequently observed in phagocytic cells using Orcein stain (Fig. 7).

DISCUSSION

The most prominent clinical feature common in Cases 1 and 2 is severe colicky pain localized in the epigastrium and the right upper quadrant of the abdomen prior to the onset of acute liver failure. Acute intraabdominal emergencies in patients with fulminant hepatitis have been reported to be associated with high fever and leukocytosis (8). Although the exact causes of severe abdominal pain in these patients remains unknown, abrupt and massive necrosis



of parenchymatous liver cells might be closely related to the abdominal pain. Marked congestion of the spleen in the two cases may be connected with the severe abdominal pain. Acute abdominal emergencies in patients with cirrhosis as in Case 1 have been reported to be due to peritonitis without a definite cause (9). Endotoxaemia due to peritonitis following intravascular coagulation may be responsible for the pathogenesis of acute liver failure (10). However, signs and symptoms of peritonitis and laboratory data supporting intravascular coagulation were not detected throughout the courses of the present three cases. Low concentration of plasma fibrinogen in Case 1 was caused by markedly decreased synthesis by extensively injured parenchymatous liver cells.

Although HBsAg occurs frequently in patients with leukemia, no difference between mean serum GPT levels of leukemia patients with and without HBsAg has been reported (1). However, asymptomatic increases in serum GPT levels in some cases of leukemic patients are observed. Even in these cases toxic liver injury by therapeutic cytotoxic agents has been reported in the literature (6). Furthermore, the fatal development of fulminant infectious hepatitis during the course of leukemia has rarely been reported. On the other hand, the fatal appearance of hepatic necrosis in leukemic patients treated with 6-MP has been described (11).

Antitumor drugs are potent therapeutic agents but impair host defense mechanisms (4). Therefore, persistence of HBsAg in leukemic patients as well as immune defects primarily associated in leukemia result from antitumor drug therapy (1). The immunosuppressive effects of chemotherapy on the cell-mediated functions may be important in HBsAg persistence (12). Galbraith *et al.* (2) have recently reported that withdrawal of cytotoxic drugs suppressing the normal immunological responses to HBsAg resulted in recovery of immunocompetence leading to rapid destruction of all HBsAg infected hepatocytes. Thus they postulated that all patients with malignant diseases treated with cytotoxic drugs should be routinely tested for HBsAg in order to identify those at risk.

From quantitative and serial determinations of HBsAg titers in myeloproliferative and lymphoproliferative disorders, Wands *et al.* (13) suggested that the administration of antitumor chemotherapeutic agents caused the appearance of HBsAg and decreased titers of HBsAb in patients with positive HBsAb. The increase in HBsAg titer was associated with hepatocellular damages, as coincidentally manifested by an elevation in serum GPT. In Case 1, continuously

Fig. 7. Liver specimen of Case 3 with acute lymphocytic leukemia and fulminant hepatic failure. a. Liver cell necrosis was extensive and only glandular cells were seen at the periphery of the lobule. They were probably abnormal ductular cells. Phagocytic cells in the lobule were prominent. Mild accumulation of lymphocytes, neutrophils and histiocytes were observed in the portal space. H-E stain, ×100. b. Some phagocytic cells were stained positive in Orcein stain. ×100.

positive HBsAb and negative HBsAg were found throughout the course. An elevation in serum transaminase activities has never been observed. No blood transfusions during the last two years and continuous administration of antitumor agent, busulfan, at an extremely low dose makes it unlikely that fulminant hepatic failure is closely related to HBsAg. Rupture of small aneurysm in intrahepatic artery or spontaneous hepatic artery thrombosis due to intrahepatic bile duct stones could not be completely ruled out in this case (14). Further examination and considerations are required for evaluating the course of hepatic necrosis in Case 1. In Cases 2 and 3, after achieving full hematological remission by prednisolone, vincristine and other antileukemic drugs, withdrawal of prednisolone may produce a release from immunosuppression resulting in development of hepatic failure by immunoreaction of HBsAg and HBsAb (15) or the interaction between the cellular immune response of the host and HBsAg in liver cells (12). The serum HBsAg became positive after remission of leukemia and γ-globulin levels in serum increased with the onset of hepatic injury. Localization of HBsAg in the liver revealed a positive reaction in the phagocytic cells, as frequently observed from other patients with fulminant hepatitis (6). Therefore, these two cases strongly suggested that HB virus infection may have resulted from frequent blood transfusions and thrived during immunosuppression. Fulminant hepatic failure might occur due to the recovered immunoreactivity during remission from leukemia.

REFERENCES

1. Sutnick, A. I., London, W. T., Blumberg, B. S., Yankee, R. A., Gerstley, B. J. and Millman, I.: Australia antigen (a hepatitis-associated antigen) in leukemia. *J. Natl. Cancer Inst.* **44**, 1241-1249, 1970.
2. Galbraith, R. M., Eddleston, A. L. W. F., Williams, R., Zuckerman, A. J. and Bagshawe, K. D.: Fulminant hepatic failure in leukemia and choriocarcinoma related to withdrawal of cytotoxic drug therapy. *Lancet* **2**, 528-530, 1975.
3. Hersh, E. M., Bodey, G. P., Nies, B. A. and Freireich, E. J.: Causes of death in acute leukemia. *J. Am. Med. Assoc.* **193**, 105-109, 1965.
4. Many, A. and Schwartz, R. S.: Drug-induced immunologic tolerance: Site of action of cyclophosphamide. *Proc. Soc. Exp. Biol. Med.* **133**, 754-757, 1970.
5. Watanabe, A., Higashi, T., Takesue, A. and Nagashima, H.: Serum amino acid imbalance and hepatic encephalopathy. Nutritional therapy of severe liver diseases by infusion of branched chain amino acids. *Jpn. J. Gastroenterol.* **75**, 466-480, 1978.
6. Shorey, J., Schenker, S., Suki, W. N. and Combes, B.: Hepatotoxicity of mercaptopurine. *Arch. Intern. Med.* **122**, 54-58, 1968.
7. Parsons-Smith, B. G., Summerskill, W. H. J., Dawson, A. M. and Sherlock, S.: The electroencephalography in hepatic coma. *Lancet* **2**, 867-871, 1957.
8. Klatskin, G.: Subacute hepatic necrosis and postnecrotic cirrhosis due to an icteric infections with the hepatic virus. *Am. J. Med.* **25**, 333-358, 1958.
9. Finlayson, G. and Roth, H. P.: Acute abdominal emergencies in patients with cirrhosis. *Arch. Surg.* **88**, 947-953, 1964.

10. Wilkinson, S. P., Arroyo, V., Gazzard, B. G., Moodie, H. and Williams, R.: Relation of renal impairment and haemorrhagic diathesis to endotoxaemia in fulminant hepatic failure. *Lancet* **1**, 521-524, 1974.
11. Clark, P. A., Hsia, Y. E. and Huntsman, R. G.: Toxic complications of treatment with 6-mercaptopurine. *Br. Med. J.* **1**, 393-395, 1960.
12. Dudley, F. J., Fox, R. A. and Sherlock, S.: Cellular immunity and hepatitis-associated Australia antigen in liver disease. *Lancet* **1**, 723-726, 1972.
13. Wands, J. R., Chura, C. M., Roll, F. J. and Maddrey, W. C.: Serial studies of hepatitis-associated antigen and antibody in patients receiving antitumor chemotherapy for myeloproliferative and lymphoproliferative disorders. *Gastroenterology* **68**, 105-112, 1975.
14. O'Connor, P. J., Buhac, I. and Balint, J. A.: Spontaneous hepatic artery thrombosis with infarction of the liver. *Gastroenterology* **70**, 599-601, 1976.
15. Almeida, J. D. and Waterson, A. P.: Immune complexes in hepatitis. *Lancet* **2**, 983-986, 1969.
16. Shikata, T. and Yoshizaki, C.: Immunopathological study on Au antigen, Au antibody and complements in fulminant hepatitis. *Acta Hepatol. Jpn.* **14**, 87-92, 1973.