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CLINICAL CASE REPORT

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Recurrent Acute Liver Failure Because of Acute Hepatitis Induced by Organic Solvents

A Case Report

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Abstract: The authors present a case of recurrent acute liver failure because of occupational exposure to organic solvents.

A 35-year-old man with a 3-week history of worsening jaundice and flu-like symptoms was admitted to our hospital. Viral hepatitis serology and autoimmune factors were negative. The authors considered liver transplantation, but the patient's liver function spontaneously recovered. Liver biopsy revealed massive infiltration of neutrophils, but the cause of the acute hepatitis was not identified. Four months after discharge, the patient's liver function worsened again. The authors considered the possibility of antinuclear antibody-negative autoimmune hepatitis and initiated steroid treatment, which was effective. Four months after discharge, the patient was admitted for repeated liver injury. The authors started him on steroid pulse therapy, but this time it was not effective. Just before the first admission, he had started his own construction company where he was highly exposed to organic solvents, and thus the authors considered organic solvent-induced hepatitis. Although urine test results for organic solvents were negative, a second liver biopsy revealed severe infiltration of neutrophils, compatible with toxic hepatitis. Again, his liver function spontaneously improved. Based on the pathology and detailed clinical course, including the patient's high exposure to organic solvents since just before the first admission, and the spontaneous recovery of his liver damage in the absence of the exposure, he was diagnosed with toxic hepatitis. The authors strongly advised him to avoid organic solvents. Since then, he has been in good health without recurrence.

This is the first report of recurrent acute liver failure because of exposure to organic solvents, which was eventually diagnosed through a meticulous medical history and successfully recovered by avoiding the causative agents. In acute liver failure with an undetermined etiology, clinicians should rule out organic solvent-induced hepatitis.

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Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, PT-INR = prothrombin time-international normalized ratio.

INTRODUCTION

Acute hepatitis is a medical condition characterized by the presence of inflammatory cells in the liver tissue.[1] Acute hepatitis results from a wide variety of causes; viral- and drug-induced hepatitis are the most common causes in adults. In Australia, Denmark, the United Kingdom, and the United States, acetaminophen use is the most common cause of acute hepatitis, whereas in Asia and some other parts of Europe, viral hepatitis predominates.[2] Acute hepatitis is also a rare complication of exposure to organic solvents. To the best of our knowledge, however, there are no reports of recurrent acute hepatitis because of chemical exposure, including organic solvents. We report a case of recurrent acute liver failure because of acute hepatitis in a construction worker with high exposure to organic solvents.

CASE PRESENTATION

A 35-year-old man with a 3-week history of progressively worsening jaundice, cough, and flu-like symptoms was initially evaluated in a local emergency room. He worked at a construction site. Liver function test results at a regular checkup 13 months before presentation were normal. He denied using alcohol, tobacco, or other recreational drugs, and had no family history of liver disease or liver cancer. Initial evaluation at his local emergency room revealed evidence of acute hepatitis, including an international normalized ratio of prothrombin time (PT-INR) of 1.62, aspartate aminotransferase (AST) level of 1107 IU/L, alanine aminotransferase (ALT) level of 1716 IU/L, total bilirubin level of 22.0 mg/dL, and alkaline phosphatase level of 478 IU/L. He was urgently transferred to our hospital for further evaluation and management of acute hepatitis, with liver transplantation anticipated. Physical examination at our hospital revealed scleral icterus and trivial lack of awareness (grade I hepatic encephalopathy),[3] but no other signs of chronic liver disease. Viral hepatitis serologies and autoimmune factors were negative. Computed tomography revealed inflammation around the portal vein, no intra- or extrabiliary ductal dilatation, and no sign of liver atrophy or splenomegaly. Hepatomegaly was suspected [total liver volume, 2227 mL (% standard liver

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volume, 149%].[4] His condition was initially stable without symptoms of fatigue, anorexia, or encephalopathy, but 2 weeks after admission, his PT-INR and serum total bilirubin level gradually increased to 2.53 and 38.0 mg/dL, respectively. Therefore, we placed him on the registration list for liver transplantation, including that from a living donor. His brother was willing to donate, and was evaluated as a living donor candidate. Soon after that, however, the patient's liver function recovered remarkably with only supportive therapy. Thus, we decided to avoid living donor liver transplantation for this patient 4 weeks after admission. The patient underwent a liver biopsy, which revealed massive infiltration of neutrophils, strongly suggesting acute hepatitis (Figure 1). The histopathologic findings did not reveal the cause of his acute hepatitis. He was discharged 8 weeks after admission when his PT-INR had recovered to 1.31 and his total bilirubin level had decreased to 9.3 mg/dL, but the cause of the acute hepatitis was not revealed. The clinical course of the first admission is shown in Figure 2A.

Four months after discharge, the patient's liver function showed worsening at a regular outpatient examination (AST level, 254 IU/L; ALT level, 420 IU/L; total bilirubin level, 1.8 mg/dL; and PT-INR, 1.19), and he was again admitted to our hospital (Figure 2B). We considered the possibility of atypical, antinuclear antibody/antismooth muscle antibody-negative autoimmune hepatitis mainly based on his recurrent clinical course in the absence of steroids, and started him on oral prednisolone (40 mg/d). After starting the prednisolone, his liver function gradually improved (AST level, 43 IU/L; ALT level, 257 IU/L; total bilirubin level, 1.1 mg/dL; and PT-INR, 1.19), and he was discharged 8 weeks after admission. After discharge, we gradually tapered the dose of prednisolone to 10 mg/d during 20 weeks.

Four months after his second discharge, the patient was again admitted to our hospital for acute liver failure, with an AST level of 617 IU/L, ALT level of 1145 IU/L, total bilirubin level of 7.7 mg/dL, PT-INR of 1.27, and grade I hepatic encephalopathy (Figure 2C). We initiated steroid pulse therapy (prednisolone 1 g for 3 days). He, however, did not respond to the treatment this time, and 2 weeks after admission, his liver function deteriorated (AST level, 210 IU/L; ALT level, 894 IU/L; total bilirubin level, 25.2 mg/dL; and PT-INR, 1.92). Computed tomography revealed apparent liver atrophy compared with the first admission (total liver volume, 1255 mL; percent standard liver volume, 84%) and increased ascites. We again considered liver transplantation, with immediate initiation of liver-supporting therapy, including glycyrrhizin, intravenous fluid loading, and ursodeoxycholic acid. His liver function somewhat recovered (AST level, 210 IU/L; ALT level, 894 IU/L; total bilirubin level, 25.2 mg/dL; and PT-INR, 1.92 at 2 weeks after the third admission) and no hepatic encephalopathy developed, but the liver atrophy did not improve. At that time, based on his repeated worsening liver function after discharge, we began to suspect toxic hepatitis because of exposure to organic solvents (eg, toluene, xylene, and epoxy resin) used in his workplace. The patient had used organic solvents for 7 years in the workplace, and had founded his own company 2 months before his first admission. A meticulous medical history revealed that he had foregone protective gloves to cut costs after starting his own company and had thus been exposed to increased doses of organic solvents with his bare hands despite strict laws requiring the appropriate management of such agents in Japan. Urine test results, including hippuric acid, methylhippuric acid, and mandelic acid, however, were negative. Another liver biopsy was performed, which revealed more severe infiltration of neutrophils compared with his previous biopsy (Figure 3), a finding compatible with toxic hepatitis. In conclusion, considering the pathology and detailed clinical course of the patient, he was diagnosed with recurrent

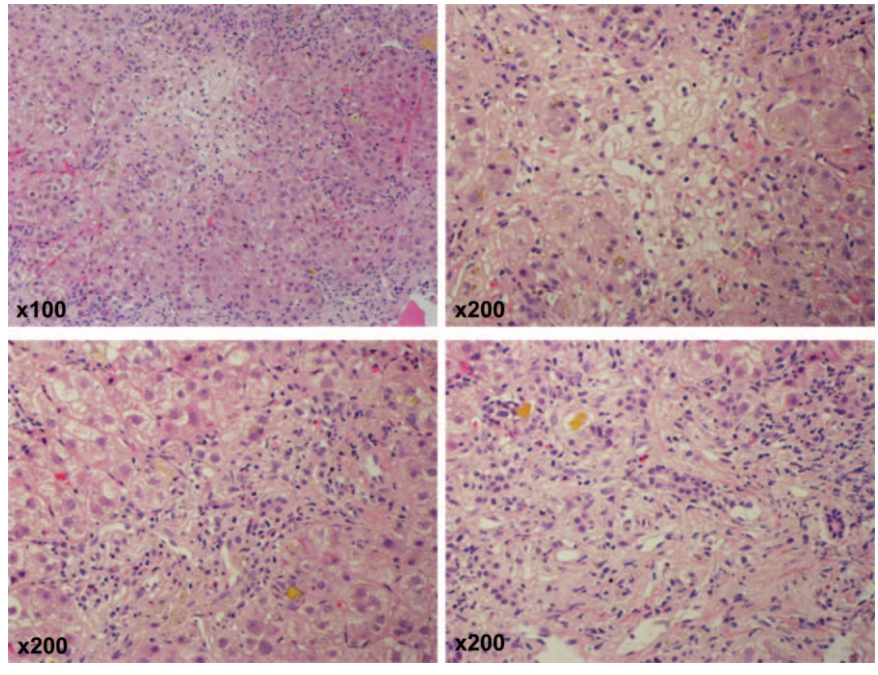

FIGURE 1. Liver biopsy results at the first admission showed massive infiltration of neutrophils.

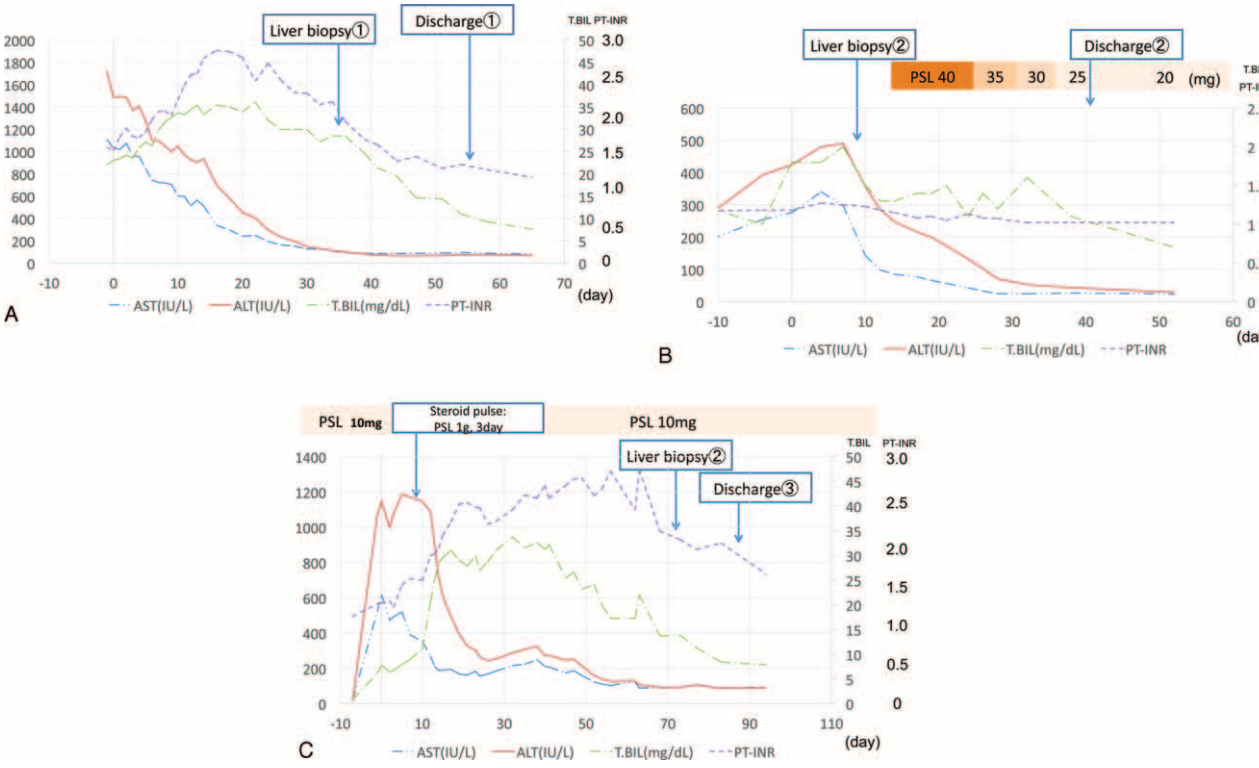

FIGURE 2. A, Clinical course of the first admission. B, Clinical course of the second admission. C, Clinical course of the third admission. ALT = alanine aminotransferase, AST = aspartate aminotransferase, PSL = prednisolone, PT = prothrombin time, TBIL = total bilirubin.

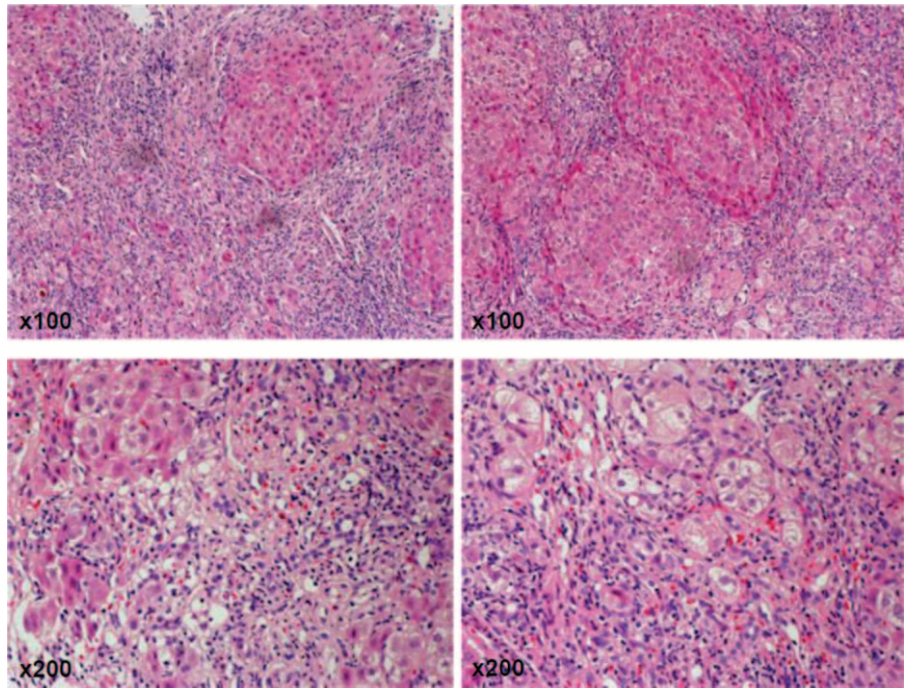

FIGURE 3. Liver biopsy results at the third admission revealed more severe infiltration of neutrophils compared with his previous biopsy.

TABLE 1. Work Up Lists for the Differential Diagnosis

Differential Diagnosis	Examination
Viral hepatitis	Viral hepatitis serology
Alcoholic hepatitis	A meticulous medical history
Autoimmune hepatitis	Autoimmune markers
	Reaction to steroid pulse therapy
	Liver biopsy
Acetaminophen	A meticulous medical history
	Acetaminophen level
Idiosyncratic drug reactions	A meticulous medical history
Budd–Chiari syndrome	Contrast enhanced computed tomography
Veno-occlusive disease	Contrast enhanced computed tomography
Ischemic liver damage	Contrast enhanced computed tomography
Malignant infiltration	Contrast enhanced computed tomography
	Tumor marker
	Liver biopsy
Sepsis	Contrast enhanced computed tomography
	Infection screening
Wilson disease	Serum chemistries
	Ceruloplasmin level
	Liver biopsy
Toxin exposure	A meticulous medical history
	Toxicology screen
	Liver biopsy

toxic hepatitis because of high exposure to organic solvents, and was strongly advised to avoid organic solvents in collaboration with the Labor, Health, and Welfare Organization. He has been in good health without recurrence for 1 year. Work up lists for etiology in this case was summarized in Table 1.

This study was approved by Graduate School of Medicine and Faculty of Medicine at the University of Tokyo Research Ethics Committee/Institutional Review Board. Written informed consent was obtained and recorded. In the preparation of this article, all efforts were made to protect patient privacy and anonymity.

DISCUSSION

We report a case of acute toxic hepatitis. Two points in this case should be emphasized. First, the patient's acute hepatitis resulted from exposure to organic solvents. Second, his acute hepatitis occurred 3 times in total, and all episodes of acute hepatitis recovered without liver transplantation. To the best of our knowledge, there is no other reported case of recurrent acute hepatitis because of organic solvent exposure.

Several studies reported on the risk of liver toxicity induced by a number of industrial chemicals including organic solvents, because most chemicals metabolized in the hepatocyte could deteriorate liver function.[5,6] It, however, is usually difficult to diagnose or even to suspect the toxic hepatitis because of occupational exposure because of its rarity.[7,8] Diagnosis of occupational toxic hepatitis generally needs 3 criteria as follows: first, liver dysfunction should occur only after occupational exposure, with the medical history of occupational exposure at workplace; second, liver enzyme levels have to be greater than at least double the upper limit of normal range; third, other causes of liver damage such as viral infection and autoimmune hepatitis have to be excluded.[8] In the current case, the patient had founded his own construction company 2 months before his first hospital admission. Since then, in an effort to reduce costs by omitting protective gloves, he had been exposed to increased doses of organic solvents with his bare hands. On admission, his liver enzyme levels were acutely elevated to greater than double the upper limit of normal. We first suspected other causes of acute hepatitis, including antinuclear antibody/antismooth muscle antibody-negative autoimmune hepatitis, which were finally excluded, and the patient was eventually diagnosed with occupational toxic hepatitis because of organic solvent exposure.

In general, testing the breath, blood, and urine for metabolites is useful for diagnosis.[9] In our case, the tests were negative. Typical pathologic findings of toxic hepatitis because of organic solvent exposure include inflammatory cell infiltrates, lipogenesis, fibrogenesis, and cholestasis.[10] In the current case, although lipogenesis and cholestasis were not observed, massive infiltration of neutrophils was prominent. Because of negative results of toxicological urinalysis and undistinctive pathologic findings, which organic solvents in toluene, xylene, and epoxy resin mainly affected was not identified in this particular case.

We usually treat acute hepatitis because of organic solvent exposure with liver-supporting therapy, including glycyrrhizin, intravenous fluids, and ursodeoxycholic acid; plasma exchange and liver transplantation may be attempted in severe cases.[11] In previous cases of acute hepatitis, 3 patients recovered spontaneously without liver transplantation, but 1 patient died of acute hepatitis before liver transplantation.[12–15] In the current case, on the patient's first and third admissions, he fulfilled the King's college criteria for liver transplantation.[16] The patient's laboratory test results indicated gradual recovery, however, and thus liver transplantation was avoided.

In conclusion, we report a case of recurrent acute liver failure caused by organic solvents. Toxic hepatitis because of organic solvents may recover spontaneously, but may also recur. Thus, it is important to consider the possibility of chemical exposure as the cause of acute liver failure as soon as possible, and to instruct the patient to avoid exposure.

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