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Troglitazone-Induced Liver Injury Diagnosed by a Laparoscopic Examination in Its Asymptomatic Stage

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Abstract A 56-year-old diabetic woman had been taking glibenclamide (10 mg daily) plus voglibose (0.6 mg daily) for recent 4 years without a successful response. Three months after troglitazone (400 mg daily) was started in addition to glibenclamide, liver dysfunction was found by chance. She demonstrated no symptoms, histological examination, however, revealed a substantial hepatocellular necrosis mainly in the peri-central vein areas, which was consistent with an idiosyncratic drug reaction. Since troglitazone -induced liver dysfunction was strongly suggested, administration of troglitazone was terminated and abnormal values of liver-chemistry returned to normal in two months.

Key words : troglitazone, diabetes mellitus, liver injury

Introduction

Troglitazone is a thiazolidine 2,4-dione derivative that represents a novel class of oral drugs for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Troglitazone decreases the elevated blood glucose levels in patients with NIDDM, especially in obese and/or insulin resistant subjects [1,2]. Unlike sulfonylureas, this hypoglycemic effect is not accompanied by enhancement of insulin secretion [1~3] and this unique mechanism may reduce the risk of hypoglycemia. Since its introduction in March 1997, more than 200,000 and 600,000 patients have received troglitazone in Japan and the United States, respectively.

In December 1997, a warning[4] on troglitazone-induced liver injury was issued, because a few patients died of hepatic failure. We recently experienced such a case, in which substantial liver cell necrosis progressed in spite of no clinical symptoms. Fortunately, the liver dysfunction was found in its early stage and abnormal values in liver -chemistry returned to normal within 2 months after discontinuation of the drug. We herein describe the case with histological examination.

Case Report

A 56-year-old woman, with a 12-year history of NIDDM, had been taking glibenclamide (10mg daily) and voglibose (0.6mg daily) for 4 years without a successful response. On August 22, 1997, troglitazone (400mg daily) was started in addition to 10mg

of glibenclamide and then voglibose was stopped. Improvement in glycemic control was not observed and hemoglobin A1c level stayed around 8.5% during subsequent 2 months. On November 20, (91st day of troglitazone therapy), 1 week prior to the expected date, she visited our out-patient clinic due to marked elevations in serum liver tests that were found on an annual physical check-up at her company. These data were in normal ranges on January 16, 1997. She was admitted to the hospital for the further evaluation in spite of demonstrating no symptoms.

On admission, aspartate transaminase (AST) level was 354 IU/L, alanine transaminase (ALT) level 844 IU/L, lactate dehydrogenase (LDH) level 689 IU/L. Total bilirubin level and alkaline phosphatase (ALP) level were within normal limits whereas γ-glutamyl transpeptidase (γ-GTP) level was 39 IU/L, slightly higher than the upper limit of normal. All other values for liver-chemistry and complete blood count were normal. She had never received any kinds of blood transfusion. Anti HA IgM, anti HBc IgM and anti-HCV antibody were negative. Titers of antibodies to cytomegalovirus, Epstein-Barr virus, herpes simplex virus and herpes zoster virus were not elevated. Anti-nuclear and anti-mitochondrial antibodies were negative. Troglitazone and glibenclamide were stopped immediately and insulin therapy was introduced. Fatty liver was first suspected since clinical symptoms were completely absent. Ultrasonography and computed tomography, however, did not demonstrate the typical findings for fat deposition. The liver-chemistry values remained high (AST 304 IU/L, ALT 725 IU/L, LDH 501 IU/L) on the 16th hospital day. Laparoscopic needle biopsy of the liver was performed on the 19th hospital day. Histological features were compatible with drug-induced idiosyncratic liver injury including hepatocellular zone 3 necrosis, acidophilic bodies in the liver cord and diffuse infiltration of lymphocytes (Fig.1). Although drug-induced lymphocyte stimulation test (DLST)

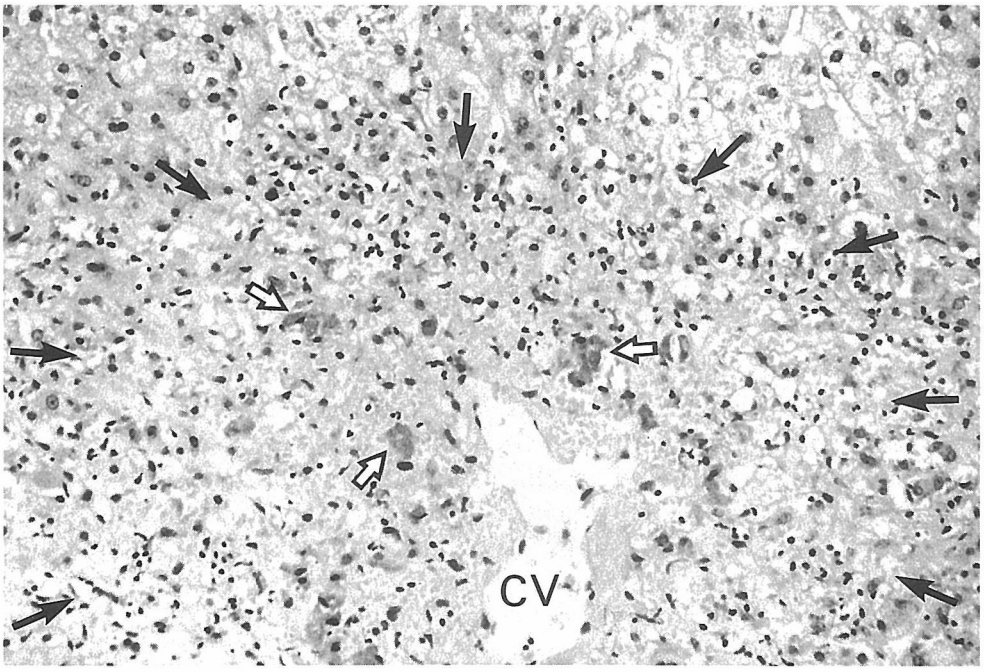

Fig.1 Necrosis in the peri-central vein area (Zone 3) is marked (indicated by black arrows), where drug metabolizing P450 enzymes are found in the highest concentration and where the oxygen tension is the lowest in sinusoidal blood. Macrophages phagocyting PAS positive necrotic substance are present (indicated by white arrows). Cholestasis is absent. (PAS stain after diastase digestion, ×400)

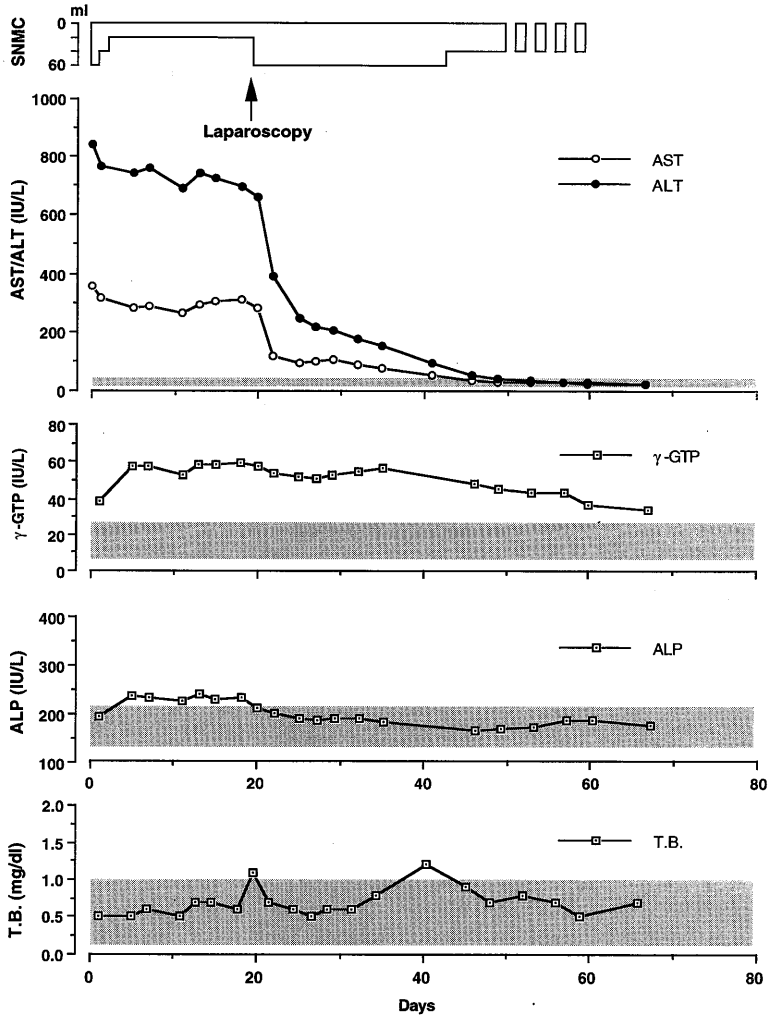

Fig.2 Clinical course and serum liver tests. Shaded areas represent the normal ranges. SNMC : Stronger Neo-Minophagen C® containing 40 mg glycyrrhizin, 20 mg cysteine and 400 mg glycine per 20 ml. T.B.: total bilirubin.

was negative, troglitazone was strongly suspected to be the causative drug of liver injury. None of autoimmune or alcoholic hepatitis was likely. She had not taken any other drugs except for glibenclamide during last 3 months before the onset of hepatic injury. Glibenclamide had been administered for 7 years without affecting serum liver tests.

A 2-month rest with injections of glycyrrhizin was required for values of AST, ALT and LDH to return to normal (Fig.2). Values of ALP and total bilirubin stayed mostly in their normal ranges whereas slight increase in levels of γ-GTP lasted during her hospital course, which finally returned to normal one month after the discharge. Insulin therapy improved her glycemic control judging from her fasting plasma glucose of 104 mg/dl and hemoglobin A1c of 7.4% on discharge.

Discussion

Watkins and Whitcomb recently reported a brief review on troglitazone-induced hepatic dysfunction[5]. On the basis of North American clinical trials of troglitazone (2,510 patients received troglitazone and 475 received placebo; 1,134 patients treated with troglitazone took the drug for at least six months), elevation in ALT level more than three times the upper limit of normal were detected in 48 (1.9%) of the troglitazone-treated patients. Twelve patients had peak ALT values more than 10 times the upper

limit of normal. In most patients, the peaks occurred between the third and seventh months of therapy (mean, 147 days), and ALT values returned to base line gradually after the discontinuation of troglitazone (mean, 55 days).

The present case appears to be a typical one in terms of the latent period and the clinical course. During preparing the manuscript, two case reports have appeared which described three diabetic patients suffered from severe hepatic dysfunction associated with troglitazone[6,7]. According to these reports, all the patients represented significant clinical symptoms related to hepatic injury when abnormal liver-chemistry values were detected. It is noteworthy that the present patient complained of no symptom at all when hepatic injury progressed substantially as shown in Fig.1. According to the prescribing information and warning[4], clinical symptoms and serum liver tests should be monitored every month during the first 6 months of therapy, then every 2 months thereafter. However, it is unknown whether this frequency of monitoring is sufficient to prevent severe liver injury, or how long this monitoring should be continued. Immediate accumulation and analyses of clinical data are required because it is not currently possible to identify prospectively the subgroup of susceptible patients to troglitazone-induced liver injury [5].

References

1) Iwamoto, Y., Kuzuya, T., Matsuda, A., Awata, T., Kumakura, S., Inooka, G., and Shiraishi, I. : Effect of new oral antidiabetic agent CS-045 on glucose tolerance and insulin secretion in patients with *NIDDM*. *Diabetes Care* **14** : 1083-1086, 1991.

2) Suter, S.L., Nolan, J.J., Wallace, P., Gumbiner, B. and Olefsky, J.O. : Metabolic effects of new oral hypoglycemic agent CS-045 in NIDDM subjects. *Diabetes Care* **15** : 193-203, 1992.

3) Fujiwara. T., Yoshioka. S., Yoshioka. T., Ushiyama, I. and Horikoshi, H. : Characterization of new oral antidiabetic agent CS-045. Studies in KK and ob/ob mice and zucker fatty rats. *Diabetes* **37** : 1549-1558, 1988.

4) American Diabetes Association. Updated statement from the American Diabetes Association about Rezulin (troglitazone) and new prescribing information/warnings. December 1, 1997.

5) Watkins, P.B. and Whitcomb, R.W. : Hepatic dysfunction associated with troglitazone. *N Engl J Med* **338** : 916-917, 1998.

6) Gitlin, N., Julie, N.L., Spurr, C.L., Lim, K.N. and Juarbe, H.M. : Two cases of severe clinical and histological hepatotoxicity associated with troglitazone, *Ann Intern Med* **129** : 36-38, 1998

7) Neuschwander-Tetri, B.A., Isley, W. L., Oki, J.C., Ramrakhiani, S., Quiason, S. G., Phillips, N.J. and Brunt, E.M. : Troglitazone-induced hepatic failure leading to liver transplantation. *Ann Intern Med* **129** : 38-41, 1998