CASE REPORT

Cirrhosis improvement to alcoholic liver fibrosis after passive abstinence

Hideaki Takahashi,[1,2,3] Ryuta Shigefuku,[1] Shiro Maeyama,[4,5] Michihiro Suzuki[1]

[1]Department of Internal Medicine, Division of Gastroenterology and Hepatology, St Marianna University, Miyamae, Kawasaki, Japan
[2]Sapporo Shirakabadai Hospital, Toyohira, Sapporo, Japan
[3]Department of Molecular Biology, Sapporo Medical University School of Medicine, Chuo, Sapporo, Japan
[4]Shiodome Medical Examination Clinic, Minato, Tokyo, Japan
[5]Department of Pathology, St Marianna University, Miyamae, Kawasaki, Japan

Correspondence to
Hideaki Takahashi,
hide-bo@marianna-u.ac.jp

HT and RS contributed equally.

SUMMARY

We present a rare case of long-term alcoholic liver disease that progressed from alcoholic liver fibrosis to alcoholic liver cirrhosis, and following passive abstinence, the patient's condition then improved to alcoholic liver fibrosis. A 70-year-old Japanese man who had consumed large amounts of alcohol since he was 20 years old received a liver biopsy for evaluation of liver dysfunction at the age of 48 in 1991. The biopsy indicated alcoholic liver fibrosis, stage 2. Eight years later, a second biopsy indicated alcoholic liver cirrhosis. The patient continued to drink until a cerebral haemorrhage in 2000 led to left hemiparesis. Thereafter, he had to accept passive abstinence. He then received follow-up liver biopsies in 2001 and 2002, both of which indicated improvement of the fibrosis.

BACKGROUND

Alcohol still accounts for a substantial proportion of liver cirrhosis cases. Some patients with alcoholic liver disease (ALD) progress to alcoholic liver cirrhosis (AL-LC) through alcoholic fatty liver (AFL) and alcoholic liver fibrosis (ALF). It is difficult for doctors and researchers to follow-up patients with ALD for long periods because of the characteristics of the patients. For a large proportion of patients with ALD, the disease state generally worsens because they decide to quit going to the hospital or continue to drink despite their hospital visit. Moreover, most of the patients with ALD can hardly abstain from drinking even if they develop AL-LC.

To our knowledge, no report on patients with ALD has confirmed development from ALF to AL-LC and improvement to ALF again by consecutive liver biopsy over a long period. We had the rare opportunity for extended observation of a patient with ALD who had progressed from ALF to AL-LC, and following passive abstinence due to cerebral haemorrhage, his condition then improved to ALF after extensive follow-up. Our observations are presented.

CASE PRESENTATION

The patient was a 70-year-old Japanese man with no history of blood transfusion. He had suffered from ALD since 1963 (at the age of 25), alcoholic chronic pancreatitis since 1991 (at the age of 48), liver cirrhosis with hepatic encephalopathy since 1999 (at the age of 56) and diabetes mellitus since 2000 (at the age of 57). In this period HBs antigen, second-generation anti-hepatitis C virus (HCV) antibody, HCV RNA, antinuclear, antibody, antismooth muscle antibody, liver kidney microsomal antibody 1 and antimitochondrial antibody were all negative. Wilson's disease and primary haemochromatosis was excluded. He underwent endoscopic mucosal resection (EMR) for early gastric cancer in 1997 and 1999 (at the ages of 54 and 56) and cerebral haemorrhage in 2000 (at the age of 57).

He consumed alcohol for more than 37 years, from the age of 20 (in 1963) to 57 (in 2000) (total ethanol consumption: approximately 2900 kg; 210 g/day). In 1991, he had undergone liver biopsy for the first time and was diagnosed with ALF 2–3 (figure 1A,B). After 8 years, he underwent a second liver biopsy and was diagnosed with AL-LC (ALF 4) with splenomegaly and collateral vessels and without esophagogastric varices and ascites (figure 1C,D). Despite the emergence of severe ALD, he continued to drink after discharge against medical advice. However, in 2000, he was forced to abstain from drinking because of a cerebral haemorrhage. Then, in 2001, he underwent a third liver biopsy and was diagnosed with ALF 3 (figure 1E,F). The following year, he underwent a fourth liver biopsy and was diagnosed with ALF 2 (figure 1G,H). Although he was transferred to our affiliated hospital, he came back to receive endoscopic submucosal dissection for early gastric cancer in 2012. And as of 2013, we confirm he is still living, although he has not desired further liver biopsies as a result of advanced age. The patient's clinical course and sequential laboratory data are shown in figure 2 and table 1, respectively.

OUTCOME AND FOLLOW-UP

Although he was transferred to our affiliated hospital, he came back to receive endoscopic submucosal dissection for early gastric cancer in 2012. As of 2013, we confirm he is still living, although he has refused further liver biopsies as a result of advanced age.

DISCUSSION

Hepatic stellate cells (HSCs) are said to play an important role in the progress of fibrosis and alcoholic metabolism.[1] Acetaldehyde contributes to the direct activation of HSCs. The addition of acetaldehyde to HSCs has been shown to increase the expression of transforming growth factor-β1 (TGF-β1) and the production of type I collagen.[2 3] Furthermore, activated Kupffer cells contribute to progression of fibrosis by initiating the production of cytokines such as TGF-β1, followed by the activation of HSCs. Acetaldehyde has also been reported to directly activate Kupffer cells.[4 5]

To cite: Takahashi H, Shigefuku R, Maeyama S, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2013-201618

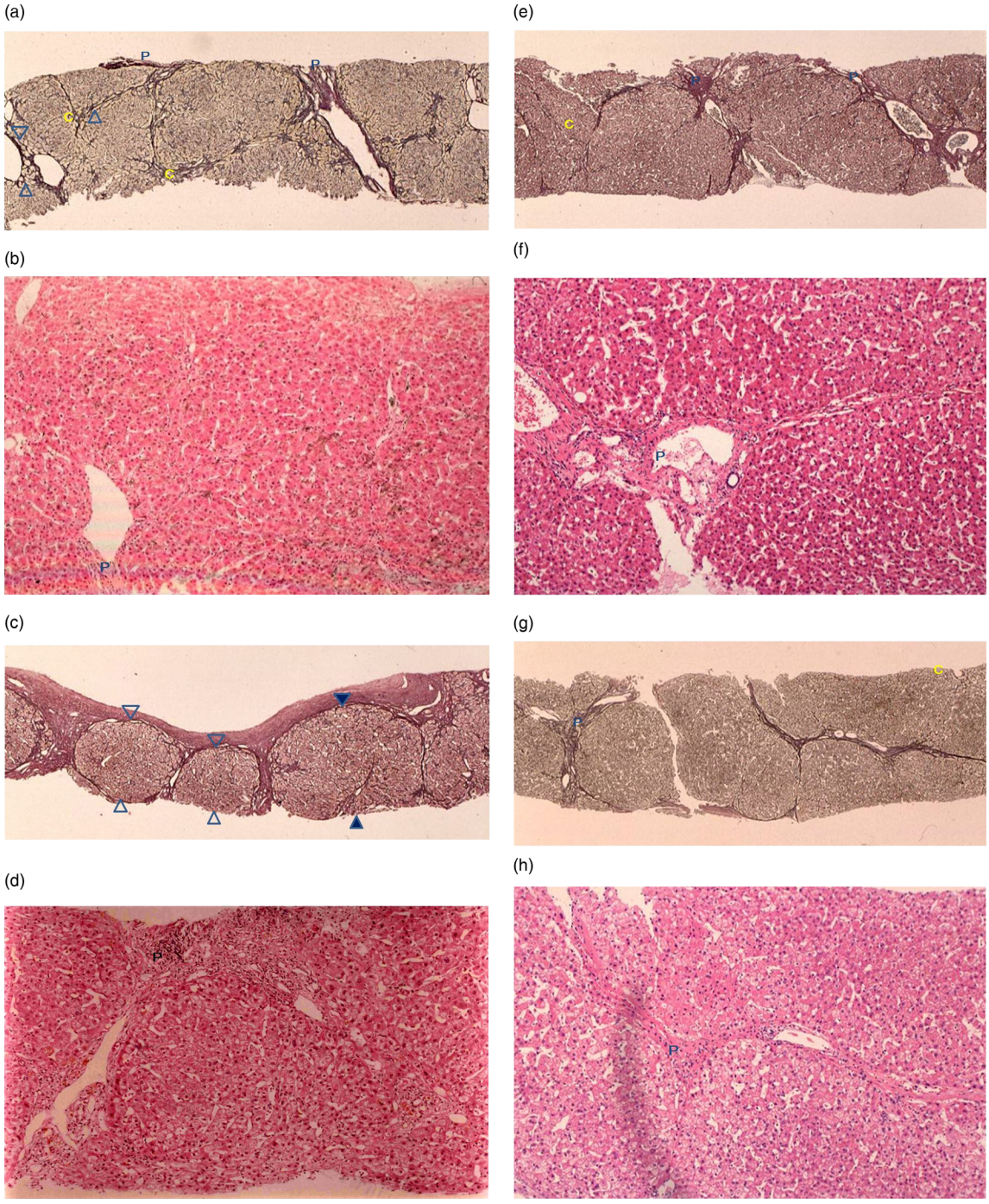

Figure 1 Sequential liver biopsies. (A) First liver biopsy. The lobular architecture is essentially preserved with P-P (portal-to-portal) and P-C (portal-to-central vein) bridgings. Fatty changes are slight deposits and pericellular fibrosis suggesting the characteristics of alcoholic liver fibrosis (ALF) is also present. The portal areas are mildly expanded mainly by fine fibre extensions. These findings correspond to alcoholic fibrosis, stage moderare to severe (ALF2-3) (P, portal area; C, central vein, △; pericellular fibrosis) (Silver impregnation, ×4). (B) First liver biopsy. Mononuclear cells are mildly infiltrated into portal areas (P) with ducule proliferations and fibrosis (H&E stain; ×10). (C) Second biopsy. Monolobular and sublobular pseudolobular formations are seen with relative thin septas. There are few focal necroses. Above, these findings correspond to alcoholic cirrhosis (△, monolobular psuedolobular formation; ▲, sublobular psuedolobular formation) (Silver impregnation, ×4). (D) Second biopsy. Moderately ballooned hepatocytes and little fatty changes are present in the parenchymas. Mononuclear cells are mildly infiltrated into the portal areas (H&E stain; ×10). (E) Third biopsy. P-P and P-C bridging fibrosis are present, but fibrotic changes are improved compared with second biopsied specimen. Perivenular and pericellular fibrosis are also present with a few necroinflammatory changes in the lobules. These histological findings correspond to alcoholic fibrosis, severe (ALF3). The fibrosis observed in the third biopsy is much improved from the second biopsy due to passive abstinence (Silver impregnation, ×4). (F) Third biopsy. Mononuclear cells are mildly infiltrated into the portal areas (H&E stain; ×10). (G) Fourth biopsy. P-P and P-C bridging fibrosis are still seen, but apparently decreased fibrotic changes, lacking of macrovesicular steatosis and pericellular fibrosis. There are focal satellite fibrosis and perivenular fibrosis. There is very mild fibrotic expansion in the portal area. The findings correspond to alcoholic liver fibrosis, moderate (ALF2) (Silver impregnation, ×4). (F) Fourth biopsy. Mononuclear cells are scattered in the portal areas with thin fibrotic expansions. Little necroinflammatory changes and fatty change in the parenchymas (H&E stain; ×10).

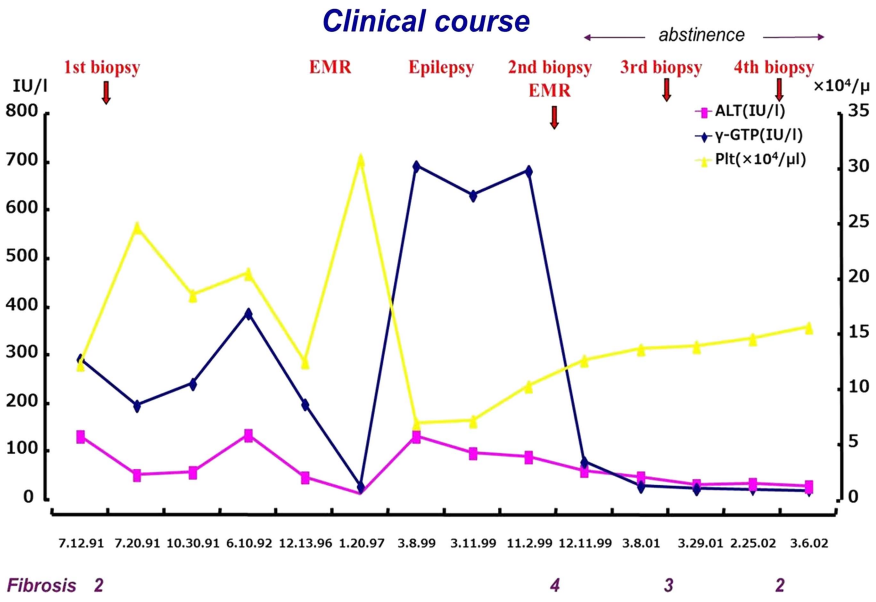

Figure 2 Clinical course.

Hepatocyte apoptosis by death receptors, hepatic inflammation and fibrosis are prominent features of liver diseases. The apoptosis of hepatocyte is important in the progress of liver fibrosis.[6] The apoptosis of hepatocyte induces inflammation. HSCs are activated by the apoptosis of hepatocyte. They reported a model of cholestatic liver injury where Kupffer cell engulfment of apoptotic bodies promotes inflammation and fibrogenesis.[7]

Excessive alcohol intake generates oxidative stress in hepatocytes; the oxidative stress then leads to liver fibrosis through the activation of HSCs. Niteo *et al*[8] reported that the addition of malondialdehyde and 4-hydroxynonenal, two oxidative stress metabolites, upregulated the production of collagen through the activation of HSCs.

The activation of Kupffer cells is suspected to be involved in the progression of fibrosis in ALD.[9] Enomoto *et al*[10] reported that this mechanism for the progression of fibrosis is associated with an enhancement of the expression of lipopolysaccharide-binding protein.

Natural killer cells induce apoptosis of activated HSCs and restrain the progression of liver fibrosis.[11 12] However, natural killer cells become non-functional in patients with ALD.[13] Hepatic fibrosis is thought to develop in patients with ALD by these mechanisms.

ALD and viral hepatitis result in very different patterns of fibrosis. In viral hepatitis, inflammation is more severe around the portal tract than in other areas. This results in the development of periportal fibrosis. In ALD, by contrast, inflammation is severe around the hepatic vein, leading to perivenular and pericellular fibrosis. Moreover, in viral hepatitis, fibrosis is thought to arise as a repair process against loss of hepatocytes. In ALD, fibrosis primarily results from the direct effect of acetaldehyde. As aforementioned, acetaldehyde in the sinusoid promotes progression of fibrosis by activating HSCs.[2 3] In chronic hepatitis C, fibrosis has been reported to improve (by 0.28±0.03 unit/year) after achievement of sustained virological response.[14] In ALD, by contrast, the great majority of patients are unable to abstain from alcohol entirely and their liver diseases gradually get worse. Moreover, it is difficult to observe patients with ALD over a long time period because most of them decide to discontinue regular outpatient visits. Therefore, there are very few reports about the improvement of fibrosis in humans.

Popper *et al*[15] used light microscopy to examine sequential liver specimens of 18 baboons exposed to alcohol on a nutritionally adequate diet for up to 6 years, as well as specimens from pair-fed controls. Furthermore, they followed up on the baboons 1 or 2 years after the period of alcohol intake. As in our case, they reported reduced fibrosis after passive complete abstinence from alcohol.

We herein report a case of ALD that progressed from ALF to AL-LC, and following a period of passive abstinence due to cerebral haemorrhage, the patient's condition improved to ALF over an extended period. We regard our case as fairly rare and valuable because such a case has not been previously reported in the literature. We conclude from our observations that abstinence may lead to improvement of fibrosis in cases of initial LC in a relatively short period without complete reconstruction of the hepatic lobule and vessel.

Table 1 Chronological changes in laboratory data.

	First biopsy 1991	Second biopsy 1999	Third biopsy 2001	Fourth biopsy 2002
Platelet count (×10⁴/μ)	12.3	10.4	13.7	14.6
Prothrombin time (%)	100	75	91	81
γ-globulin (%)	15.9	19.6	16.5	15
Hyaluronic acid (ng/mL)	—	139.0	51.4	44.6
Albumin (g/dL)	3.8	4.6	4.7	5.1
Total bilirubin (mg/dL)	1.4	1.1	1.0	1.0
AST (IU/l)	131	170	35	26
ALT (IU/l)	134	90	48	35
AST/ALT ratio	0.98	1.89	0.73	0.74
GGT (IU/l)	292	683	30	21
Total cholesterol (mg/dL)	113	97	175	144
ICG R15 (%)	7	19	11	7

ALT, alanine transaminase; AST, aspartate aminotransferase; ICG R15, indocyanine green retention rate after 15 min.

Learning points

- For many reasons, it is difficult to follow-up patients with alcoholic liver disease for long periods.
- The great majority of patients with alcoholic liver disease (ALD) are unable to abstain from alcohol entirely, and their liver diseases gradually get worse.
- To our knowledge, no report on patients with ALD has confirmed development from alcoholic fatty liver (ALF) to alcoholic liver cirrhosis and improvement to ALF again by consecutive liver biopsy over a long period.
- Our observations suggest that abstinence may lead to improvement of fibrosis in cases of initial liver cirrhosis in a relatively short period without complete reconstruction of the hepatic lobule and vessel.

Contributors HT and RS were involved in the acquisition of data. HT also drafted the manuscript and was involved in the study concept and design. SM and MS were involved in the critical review of the manuscript for important intellectual content. SM and RS provided the technical or material support. MS was involved in the study supervision.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Friedman SL. Stellate cell activation in alcoholic fibrosis—an overview. *Alcohol Clin Exp Res* 1999;23:904–10.
2 Greenwel P, Dominguez-Rosales JA, Mavi G, *et al*. Hydrogen peroxide: a link between acetaldehyde-elicited alpha1(I) collagen up-regulation and oxidative stress in mouse hepatic stellate cells. *Hepatology* 2000;31:109–16.
3 Svegliati-Baroni G, Inagaki Y, Rincon-Sanchez AR, *et al*. Early response of alpha2 (I) collagen to acetaldehyde in human hepatic stellate cells is TGF-beta independent. *Hepatology* 2005;42:343–52.
4 Matsuoka M, Tsukamoto H. Stimulation of hepatic lipocyte collagen production by Kupffer cell-derived transforming growth factor beta: implication for a pathogenetic role in alcoholic liver fibrogenesis. *Hepatology* 1999;11:599–605.
5 Pastrino JG, Shulga N, Hoek JB. TNF-alpha-induced cell death in ethanol-exposed cells depends on p38 MAPK signaling but is independent of Bid and caspase-8. *Am J Physiol Gastrointest Liver Physiol* 2003;285:G503–16.
6 Ishii H, Adachi M, Fernández-Checa JC, *et al*. Role of apoptosis in alcoholic liver injury. *Alcohol Clin Exp Res* 2003;27:1207–12.
7 Canbay A, Feldstein AE, Higuchi H, *et al*. Kupffer cell engulfment of apoptotic bodies stimulates death ligand and Cytokine expression. *Hepatology*2003;38:1188–98.
8 Nieto N, Friedman SL, Cederbaum AI. Cytochrome P450 2E1-derived reactive oxygen species mediate paracrine stimulation of collagen I protein synthesis by hepatic stellate cells. *J Biol Chem* 2002;277:9853–64.
9 Hoek JB. Endotoxin and alcoholic liver disease: tolerance and susceptibility. *Hepatology* 1999;29:1602–4.
10 Enomoto N, Ikejima K, Bradford BU, *et al*. Alcohol causes both tolerance and sensitization of rat Kupffer cells via mechanisms dependent on endotoxin. *Gastroenterology* 1998;115:443–51.
11 Redaeva S, Sun R, Jaruga B, *et al*. Natural killer cells ameliorate liver fibrosis by killing activated stellate cells in NKG2D-dependent and tumor necrosis factor-related apoptosis-inducing ligand-dependent manners. *Gastroenterology* 2006;130:435–52.
12 Freidman SL. Mac the knife? Macrophages-the double-edged sword of hepatic fibrosis. *J Clin Invest* 2005;115:29–32.
13 Jeong WI, Park O, Gao B. Abrogation of the antifibrotic effects of natural killer cells/interferon-gamma contributes to alcohol acceleration of liver fibrosis. *Gastroenterology* 2008;134:248–58.
14 Shiratori Y, Imazeki F, Moriyama M, *et al*. Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. *Ann Int Med* 2000;132:517–24.
15 Popper H, Lieber CS. Histogenesis of alcoholic fibrosis and cirrhosis in the baboon. *Am J Pathol* 1980;98:695–716.