Two Cases of Non-Alcoholic Steato-Hepatitis Developing from Simple Fatty Liver

Soo Ryang Kim, Taisuke Nakajima, Kenji Ando, Keiji Mita, Katsumi Fukuda

Department of Gastroenterology, Kobe Asahi Hospital, Kobe, Japan.

Abstract

We describe two cases of non-alcoholic steatohepatitis (NASH) developing from simple fatty liver and detected by histological examination in two women. In both cases hypertension and diabetes mellitus showed no exacerbation during follow-up; hepatitis C antibody and hepatitis B surface antigen were negative; ultrasound (US) and computed tomography (CT) revealed fatty liver (moderate in one patient and severe in the other). Body mass index (BMI) was 48 and 44 in 2004 and 2007, respectively, in one and 24 in both 2006 and 2007, respectively, in the other. Liver function tests showed some fluctuation in aspartate aminotransferase and alanine aminotransferase. The first US-guided liver biopsy showed simple fatty liver; the second biopsy after two and a half years on one patient and one and a half years on the other, revealed histological features of NASH characterized by predominantly macrovesicular fatty change (40% in one and 80% in the other) with occasional ballooning, fibrosis (moderate in one and slight in the other) extending from zone 3 to zone 1, intra-acinar inflammation with neutrophil infiltration, and mild portal chronic inflammation with piecemeal necrosis. Fibrosis progressed from stage 0 to stage 2 in two and a half years in one patient, and from stage 0 to stage 1 in one and a half years in the other. Clinicians should be vigilant during the clinical course of NASH developing from simple fatty liver.

Key words

Non-alcoholic steatohepatitis – simple fatty liver – body mass index – fibrosis – macrovesicular fatty change – ballooning.

Introduction

Estimates based on imaging and autopsy studies suggest that about 20-30% of adults in the United States, other Western countries [1] and Japan [2] have excess fat accumulation in the liver. Non-alcoholic fatty liver disease (NAFLD) is currently defined as the accumulation of fat in the liver exceeding 5-10% by weight, but is estimated practically as the percentage of fat-laden hepatocytes observed microscopically [3]. About 10% of such individuals, or fully 2-3% of adults, are estimated to meet current diagnostic criteria for non-alcoholic steatohepatitis (NASH).

NAFLD has a spectrum ranging from fatty liver alone to steatohepatitis, steatonecrosis, and NASH [4-8]. Although fatty liver alone is considered nonprogressive [7, 8], patients with NASH can develop progressive liver disease and cirrhosis. Histologically, NASH is similar to alcohol-induced hepatitis [7]. The diagnostic criteria for NASH continue to evolve and rely on the histologic findings of macrovesicular steatosis, mixed inflammatory cell infiltration of lobules, hepatocellular injury (ballooning, Mallory bodies), and perisinusoidal fibrosis or cirrhosis [7, 9-13]. Generally recognized indications for biopsy include establishing the diagnosis and staging the injury, but there are no strict guidelines.

Here we describe two cases of NASH developing from simple fatty liver.

Case 1

A 48-year-old woman was admitted to Kobe Asahi Hospital in November 2004 for histological examination of fatty liver. She had no history of alcohol intake, but had a history of hypertension and diabetes mellitus, and was taking glimepiride (2 tabs) and metformin hydrochloride (2 tabs) for diabetes, and amlodipine besilate (2 tabs) for hypertension. Her height was 151 cm, body weight 110 kg, and body mass index (BMI) 48. Laboratory data disclosed the following values: aspartate aminotransferase (AST) 20 IU/l (normal 10-40), alanine aminotransferase (ALT) 18...
IU/ml (5-40), fasting blood sugar (FBS) 121 mg/dl (70-109), hemoglobin A1c (HbA1c) 6.6% (4.3-5.8), hyaluronic acid 41 ng/ml (≤50), Hb (hemoglobin) 10.8 g/dl (11.3-15.2), white blood cells (WBC) 7300/μl (3500-9100) and platelets (PLT) 23.8×10⁴/μl (13.0-36.9). The serum was negative for hepatitis C virus antibody (anti-HcV) and hepatitis B surface antigen (HBsAg). Both ultrasound (US) and plain computed tomography (CT) disclosed fatty liver, and the liver spleen ratio (L/S ratio) was 0.87. US-guided biopsy revealed simple fatty liver characterized by fatty change of up to 20% without ballooning, no fibrosis (stage 0), no intraacinar inflammation, and no portal chronic inflammation (Fig. 1). From 2004 until 2007, AST fluctuated from 14 to 126 IU/ml and ALT from 12 to 41 IU/ml (Fig. 2). The patient had not taken any antioxidants such as vitamin E or ursodeoxycholic acid. On readmission in May 2007 for histological examination of the liver, body weight was 100kg, and BMI 44. Laboratory data disclosed the following values: AST 50 IU/l, ALT 27 IU/l, FBS 85 mg/dl, HbA1c 7.2%, hyaluronic acid 111 ng/ml, WBC 5300/μl and PLT 21×10⁴/μl. Plain CT revealed severe fatty liver with an L/S ratio of 0.75. US-guided biopsy revealed NASH characterized by predominantly macrovesicular fatty change (40%), with occasional ballooning, moderate fibrosis (stage 2) extending from zone 3 to zone 1, intraacinar inflammation with neutrophil infiltration, and mild portal chronic inflammation with piecemeal necrosis (Figs. 3a, b).
Case 2

A 62-year-old woman with no history of alcohol intake had a history of hypertension and diabetes. She was taking glimepiride (1 tab) for diabetes mellitus, and valsartan (1 tab) and amlodipine (2 tabs) for hypertension. Her height was 144 cm, body weight 49kg, and BMI 24. Laboratory data on admission in January 2006 disclosed the following values: AST 25 IU/l, ALT 31 IU/ml, FBS 109 mg/dl, HbA1c 6.3%, hyaluronic acid ≤9 ng/ml, Hb 12.8 g/dl, WBC 4800/μl and PLT 18.8×10^4/μl. The serum was negative for anti-HCV and HBsAg. US and CT disclosed fatty liver with an L/S ratio of 0.70. US-guided biopsy revealed simple fatty liver characterized by fatty change up to 60% with no fibrosis (stage 0), no intraacinar inflammation, and no portal chronic inflammation (Fig. 4). From 2006 until 2007, liver function tests fluctuated: AST from 20 to 35 IU/ml and ALT from 24 to 61 IU/ml (Fig. 5). In September 2007, she was readmitted for histological examination for liver dysfunction. Her body weight was 50kg, and BMI 24. Laboratory data disclosed the following values: AST 35 IU/l, ALT 58 IU/l, FBS 86 mg/dl, HbA1c 6.4%, hyaluronic acid 19 ng/ml, WBC 6100/μl and PLT 19.0×10^4/μl. Plain CT revealed severe fatty liver with an L/S ratio of 0.70. US-guided biopsy revealed NASH characterized by predominantly macrovesicular fatty change (80%) with occasional ballooning, slight fibrosis (stage 1) extending from zone 3 to zone 1, intraacinar inflammation with neutrophil infiltration, and mild portal chronic inflammation with piecemeal necrosis (Fig. 6).

Fig 4. Histological features of US-guided biopsy of the liver (case 2; first biopsy). Simple fatty liver characterized by up to 60% fatty change without ballooning, no fibrosis (stage 0), no intraacinar inflammation, and no portal chronic inflammation (January 2006) (a) HE stain (x100) (b) Mallory-Azan stain (x 100).

Fig 5. Aminotransferase levels from 2006 to 2007.

Fig 6. Histological features of US-guided biopsy of the liver (case 2; second biopsy). NASH characterized by predominantly macrovesicular fatty change (80%) with occasional ballooning, slight fibrosis (stage 1) extending from zone 3 to zone 1, intraacinar inflammation with neutrophil infiltration, and mild portal chronic inflammation with piecemeal necrosis (September 2007) (a) HE stain (x100), (b) Mallory-Azan stain (x 200).
Discussion

How NASH is best defined remains unsettled because of significant diversity of opinion among expert pathologists regarding the necessity of testing and the features of specific findings [14].

A NAFLD classification system has also been proposed that correlates certain histologic features with long-term prognosis (these groups are identified variably by class or type) [4]. Class 1 constitutes simple steatosis, class 2 is steatosis with lobular inflammation, class 3 requires the additional presence of ballooned hepatocytes, and class 4 requires the presence of either Mallory’s hyaline or fibrosis. Within this system, class 3 and 4 NAFLD are similar and might be considered a single group constituting NASH. Currently, the aggressive form of NAFLD is best based on the pathological diagnosis of steatonecrosis with Mallory’s hyaline and fibrosis. Class 2 NAFLD is more controversial; it may be benign and includes relatively more men, often with a normal BMI.

Class 3-4 NAFLD or NASH is described further by using 4 stages of fibrosis. A separate group of adult patients with primarily periportal fibrosis has been described, but this variant is not yet established as a distinct entity. Stage 4 NASH has been suggested to include NASH with cirrhosis, cirrhosis with features of NASH, and cryptogenic cirrhosis. It is now accepted that cryptogenic cirrhosis may represent a late phase of NASH that has lost the typical necroinflammatory and steatotic features in up to 80% of patients [11, 15-17].

Furthermore, liver-related deaths are the second most common cause of death in NAFLD, with rates equaling those of death from coronary artery disease and trailing only cancer-related deaths [15].

The adverse outcomes of cirrhosis and liver-related deaths are more common in the types of non-alcoholic fatty liver with necrosis than in those without necrosis. This finding is particularly important because within the spectrum of NAFLD the histological parameters of necrosis are interpreted more reliably than those of inflammation [6].

Why some patients with NAFLD progress to fibrosis and cirrhosis and others generally have a benign course without progressive clinical or histological sequelae is unclear. One concept for the initiation of necroinflammation suggests a two-hit process: accumulation of excessive fat and development of oxidative stress. Both steps result in the production of lipid peroxidation products (malondialdehyde and 4-hydroxynonenal) that are probably involved in the stimulation of collagen production, fibrosis, and cirrhosis [5, 6, 18, 19].

Liver biopsy is the only means of assessing the presence and extent of specific necroinflammatory changes and fibrosis. Firm recommendations of when to conduct a liver biopsy in the routine clinical setting have not yet been developed, however, and care will continue to require individualization [1].

Until now the degree of sampling error has not been adequately studied. It is possible that the first biopsy samples in our cases might have been sampling errors; however, the liver biopsies were reassessed and the finding of NASH developing from simple fatty liver was confirmed. In case 1, fibrosis progressed from stage 0 to stage 2, while in case 2 it progressed from stage 0 to stage 1. This may reflect only the period between the two liver biopsies, i.e. 31 months in case 1 and 21 months in case 2. In NASH the speed of progressing fibrosis remains to be clarified, whereas in HCV, the speed of progressing fibrosis is 0.1 unit/year [20]. The speed of progressing fibrosis should have been continuously observed in our two cases.

From the above observations, two questions have arisen. First, is only one liver biopsy enough to obtain a precise diagnosis in cases of NAFLD? Although the diagnosis of simple fatty liver is reached by liver biopsy, it may change at a later date. In other words, second hits could occur in simple fatty liver in NASH cases with a benign clinical course. The patients’ BMI improved (from 48 to 44) in case 1 and did not change (from 24 to 24) in case 2 during the follow-up period. Second, what is the second hit in NASH cases that develop from simple fatty liver whose functions have fluctuated to some extent?

Further study is needed to clarify the indications for repeated biopsies for NAFLD cases and the pathogenesis of NASH, especially with respect to second hits.

References

NASH developing from simple fatty liver