Nonalcoholic Steatohepatitis with Improved Hepatic Fibrosis after Weight Reduction

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Abstract

A 65-year-old woman was admitted to our hospital for an investigation of liver dysfunction. She had mild obesity with hyperlipidemia, but no history of alcohol abuse. Other known causes of liver dysfunction, such as viruses, autoimmunity and drug effects, were excluded. The liver histology was consistent with nonalcoholic steatohepatitis (NASH). After diagnosis of NASH, the patient started diet and exercise therapy and, in parallel with weight reduction, her liver function improved. One year after the therapy, a liver biopsy showed that steatosis, necroinflammation and even fibrosis were improved. Hence, here we report a case of NASH in which weight reduction was effective in improving both biochemical and histological findings.
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Key words: nonalcoholic steatohepatitis, weight reduction, hepatic fibrosis

Introduction

Obesity is an epidemic that is currently recognized as a major public health problem worldwide. In recent years, the number of obese patients has also increased in Japan. Obesity is a risk factor for various diseases such as type II diabetes, hyperlipidemia, hypertension and cardiovascular disease. Furthermore, obesity is a condition that is often reported in association with nonalcoholic fatty liver diseases, including nonalcoholic steatohepatitis (NASH) (1–4).

NASH is a condition characterized by a histologic picture similar to alcoholic liver injury, but without the presence of alcohol abuse (1–4). Many patients with NASH have underlying risk factors such as obesity, diabetes mellitus and hyperlipidemia (1–5). The natural history and the long-term prognosis of NASH are not well understood, but the available data suggest that NASH is a benign disease in most patients. However, it was reported that 43% of patients with NASH had histologic progression and in approximately 8% to 17% of patients with NASH it can lead to cirrhosis with related complications (6–8).

There are a few previous reports on the effect of diet and exercise therapy on the clinical features of NASH (9–12). However, the effect of weight reduction on histologic findings, and especially on fibrosis, is not fully understood. Several drug therapies for NASH have been reported to be potentially useful, but the number of patients in these studies was small. Here, we describe a patient with NASH who was treated using diet and exercise therapy, and consequently showed both biochemical and histologic improvement of the liver.

Case Report

The patient was a 65-year-old woman who had suffered from liver dysfunction from 1998. She had no history of blood transfusion, or alcohol or drug abuse. Although she had received injections of 60 ml of stronger neo-minophagen C (SNMC) three times a week, her elevated transaminase levels were sustained. She was admitted to our hospital on May 9, 2001 for an examination of her liver dysfunction. A physical examination on admission showed mild obesity (body mass index; BMI 25.1 kg/m^2). No hypertension or hepatomegaly were noted. The laboratory data on admission are shown in Table 1.

Blood biochemistry tests showed an aspartate aminotransferase (AST) level of 210 IU/*l*, alanine aminotransferase (ALT) 231 IU/*l*, lactate dehydrogenase (LDH) 293 IU/*l* and alkaline phosphatase (ALP) 385 IU/*l*. The fasting blood glu-

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Table 1. Laboratory Data on Admission

Peripheral blood		Blood Chemistry			
White blood cells	4,900/mm^3	Total protein	8.1 g/dl	Iron	125 μg/dl
Neutorophil	57%	Albumin	5.1 g/dl	Ferritin	225.3 ng/dl
Eosinophil	3%	Total bilirubin	1.2 mg/dl	Copper	101 μg/dl
Basophil	0%	Asparate aminotransferase	210 IU/*l*	Ceruloplasmin	22.4 mg/dl
Lymphocyte	29%	Alanin aminotransferase	231 IU/*l*	Serology	
Monocyte	11%	Alkaline phosphatase	385 IU/*l*	Immunoglobulin G	1150 mg/dl
Red blood cells	474×10^4/mm^3	Lactate dehydrogenase	293 IU/*l*	Immunoglobulin A	64 mg/dl
Hemoglobin	14.8 g/dl	γ-glutamyltranspeptidase	68 IU/*l*	Immunoglobulin M	642 mg/dl
Hematocrit	42.50%	Blood urea nitrogen	15 mg/dl	HBsAg	0.1 COI
Platelet	16.0×10^4/mm^3	Creatinine	0.7 mg/dl	HBc-Ab	96.2%
Coagulation		Na	145 mEq/*l*	HBcAb (×200)	16.1%
Prothrombin time	94%	K	4.1 mEq/*l*	Anti-HCV antibody	(–)
APTT	29.9 sec.	Cl	109 mEq/*l*	HBV DNA	(–)
		Total cholesterol	231 mg/dl	HEV RNA	(–)
		Triglyceride	155 mg/dl	TTV DNA	(–)
		Blood glucose	86 mg/dl	Antinuclear antibody	(–)
		HbA1c	4.7%	Antimitochondral antibody	(–)
		Fasting insulin	13.2 μU/ml	Antismooth muscle antibody	(–)
		HOMA	2.8		
		ACE	25.9 IU/*l*		

ATT: activated partial thromboplastine time, HOMA: homeostasis model of assessment, ACE: angiotensin converting enzyme, HBsAg: hepatitis B surface antigen, HBc-Ab: anti-hepatitis B core antibody, HCV: hepatitis C virus, COI: cut off index, HBV: hepatitis B virus, HEV: hepatitis E virus, TTV: TT virus, DNA: deoxyribonucleic acid, RNA: ribonucleic acid.

cose, hemoglobin A1c and fasting insulin levels were all normal. The patient's homeostasis model of assessment (HOMA) score (13), which is commonly used as a surrogate marker for insulin resistance, was elevated to 2.80. Total cholesterol and triglyceride levels were elevated to 231 mg/dl and 155 mg/dl, respectively. The patient tested negative for various viral markers, including hepatitis B surface antigen (HBs-Ag), anti-hepatitis B core antibody (HBc-Ab), antibody to hepatitis C virus (anti-HCV), HBV DNA, TT virus (TTV) DNA and hepatitis E virus (HEV) RNA. HBsAg, and HBc-Ab were assayed using commercially available radioimmunoassay kits (Dainabot, Tokyo, Japan). Anti-HCV was determined using a third-generation enzyme-linked immunoadsorbent assay (Ortho Diagnostics Systems, Tokyo, Japan). Serum HBV DNA was tested by using polymerase chain reaction (PCR) reported previously (14), TTV DNA was tested by using PCR kit (Institute of Immunology Co., Ltd. Tokyo, Japan) and HEV RNA was tested by RT-PCR (Mitsubishi Kagaku Bio-Clinical Laboratories, Inc. Tokyo, Japan). Autoantibodies, including anti-nuclear antibody (ANA), anti-mitochondrial antibody (AMA), and anti-smooth muscle antibody (ASMA) were also negative. The autoimmune hepatitis (AIH) score by the revised international criteria (15) for diagnosis of AIH was nine, which was not considered to be AIH. Serum iron, copper, ceruloplasmin and angiotensin-converting enzyme level were normal. Fibrosing markers, hyaluronic acid and procollagen III peptide (P-III-P) were elevated (hyaluronic acid 186 ng/ml, normal range ≤50 ng/ml; P-III-P 1.4 U/ml, normal range ≤1.0 U/ml). An ultrasonography examination suggested that the echogenicity of the liver was diffusely increased, compared to that of the kidneys. A liver biopsy was performed on the fourth hospital day to evaluate liver histology. A specimen evaluated using light microscopy showed the presence of macrovesicular and microvesicular steatosis, spotty necrosis, mild to moderate inflammatory cell infiltration and moderate perivenular, perisinusoidal and portal fibrosis (Fig. 1) with one focus of porto-portal bridging fibrosis [Grade 2 and Stage 3, as categorized by Brunt et al. (16)]. Based on these findings, the patient was diagnosed with nonalcoholic steatohepatitis (NASH).

After diagnosis of NASH, diet therapy (1,280 kcal/day; 25 kcal/kg/day) and exercise therapy (180 kcal/day) was started. The patient made a continuous effort toward achieving weight reduction. Consequently, her body weight decreased from 58 kg to 53 kg (BMI 22.9 kg/m^2) and her elevated level of transaminases normalized after 12 months of diet and exercise therapy, in parallel with her weight reduction (Fig. 2). However, the patient's HOMA score did not decrease (HOMA 3.0).

On July 15, 2002, the patient was re-admitted to our hospital for examination of her liver and a second liver biopsy was performed. Compared with the initial biopsy, histologic findings such as steatosis, necroinflammation and even fibrosis of the liver, were improved (Fig. 3: Grade 1 and Stage 2). Based on laboratory data, hyaluronic acid and P-III-P had normalized to 28.2 ng/ml and 0.9 U/ml, respectively.

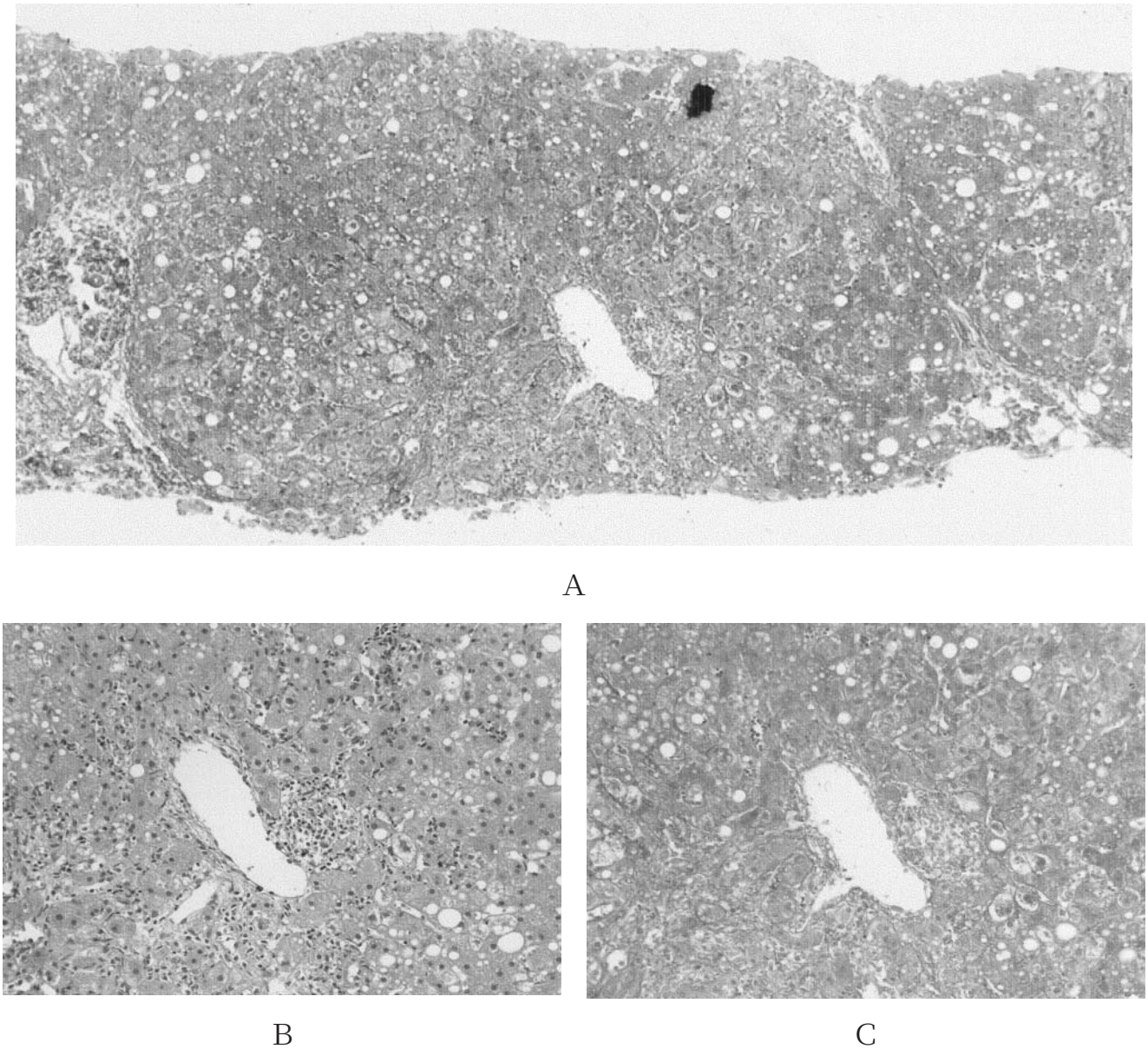

Figure 1. Liver biopsy specimens before diet and exercise therapy. A. Moderate macrovesicular and microvesicular steatosis, and moderate fibrosis in the centrilobular and portal areas (Azan-Mallory, ×40). B. Moderate steatosis, spotty necrosis with lymphocyte and polymorphonuclear leukocyte infiltration and ballooned hepatocytes around the central vein (hematoxylin and eosin, ×100). C. Extensive perivenular and perisinusoidal fibrosis in the centrilobular (zone 3) area (Azan-Mallory, ×100).

Discussion

NASH is defined histologically when a combination of macrovesicular steatosis, hepatocyte injury and necrosis, mixed inflammatory cell infiltration and variable degrees of fibrosis are observed in the absence of chronic abuse of alcohol (1–4). The histologic findings for the patient described above were consistent with NASH, showing 30 to 50% macrovesicular and microvesicular steatosis, porto-portal bridging fibrosis, piecemeal necrosis, and mild-to-moderate inflammatory cell infiltration. NASH is mainly associated with obesity and diabetes mellitus, hypercholesterolemia and hypertriglyceridemia (1–5), and the patient also had some of these risk factors.

Although in most cases fatty liver disease does not progress to more severe liver diseases, approximately 20 to 30% of patients have histologic signs of fibrosis and necroinflammation, indicating the presence of NASH. Furthermore, some cases of NASH are at a higher risk of developing cirrhosis, terminal liver failure, and hepatocellular carcinoma (7, 8, 17, 18). It has been reported that obese persons of relatively advanced age (≥45 years), and those with diabetes mellitus, a greater degree of hepatic steatosis, and higher grades of hepatic inflammation have a risk for progression to

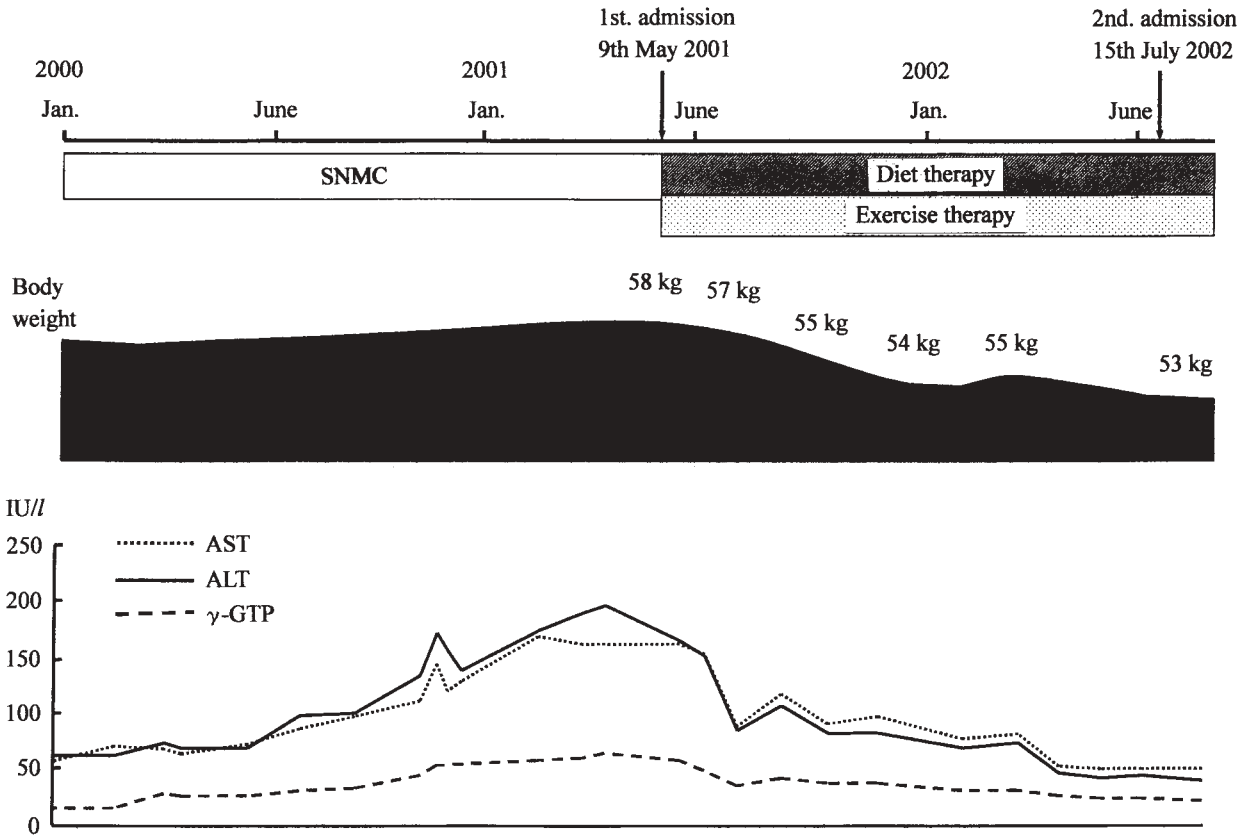

Figure 2. The clinical course of the patient. In parallel with weight reduction, liver dysfunction improved during diet and exercise therapy. AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyltransferase, P-III-P: procollagen III peptide.

cirrhosis (19).

Current treatments for NASH are unproven. Improvement of liver chemistry, but variable changes in histology, have been reported after weight reduction in a small number of patients with NASH (9–11). The rate of weight reduction is important and may play a critical role in determining whether liver histologic findings improve or worsen. Rapid weight reduction has been associated with exacerbation of steatohepatitis in obese patients, and histologic exacerbation has been observed when the rate of weight reduction exceeded 1,600 g per week (20). Hence, weight reduction should be moderate and should also be monitored carefully. However, the most effective rate of weight reduction still has to be established. In the current case, the patient achieved 5 kg weight reduction during one year of diet and exercise therapy. Originally elevated transaminase levels decreased in parallel with this weight reduction. Furthermore, an improvement in liver histology, including the grade of steatosis, inflammation and the stage of fibrosis, were observed after weight reduction. These findings indicate that weight reduction is a useful therapy for NASH, but large prospective studies are needed to confirm this suggestion.

The mechanisms by which weight reduction improves hepatic inflammation and fibrosis in NASH patients remain unclear. The pathogenesis of NASH is multifactorial. In a model for the development of NASH (21), it is suggested that insulin resistance is an important factor in the accumulation of hepatocellular fat. Other factors, such as genetic mutations, excess carbohydrates, drugs and toxins may also contribute to hepatic steatosis. An excess of fat in the liver predisposes some individuals to hepatocellular injury, caused by the direct cellular toxicity of excess free fatty acids, oxidative stress and lipid peroxidation, or other mechanisms. Although, it is commonly known that diet and exercise therapy alter insulin sensitivity, the current patient showed no significant change in insulin resistance during therapy. These findings might suggest that hepatic steatosis does not depend on insulin resistance only.

Drugs such as gemfibrozil (22), ursodeoxycholic acid (23), vitamin E (α-tocopherol) (24) and metformin (25) have been shown to be promising treatments for NASH. However, studies of these drugs have been limited to only small numbers of patients, and they have also had variation in the definition of NASH and insufficient evaluation of treatment outcomes. In addition, medical therapies for NASH have had other problems, such as costs and side effects. While the es-

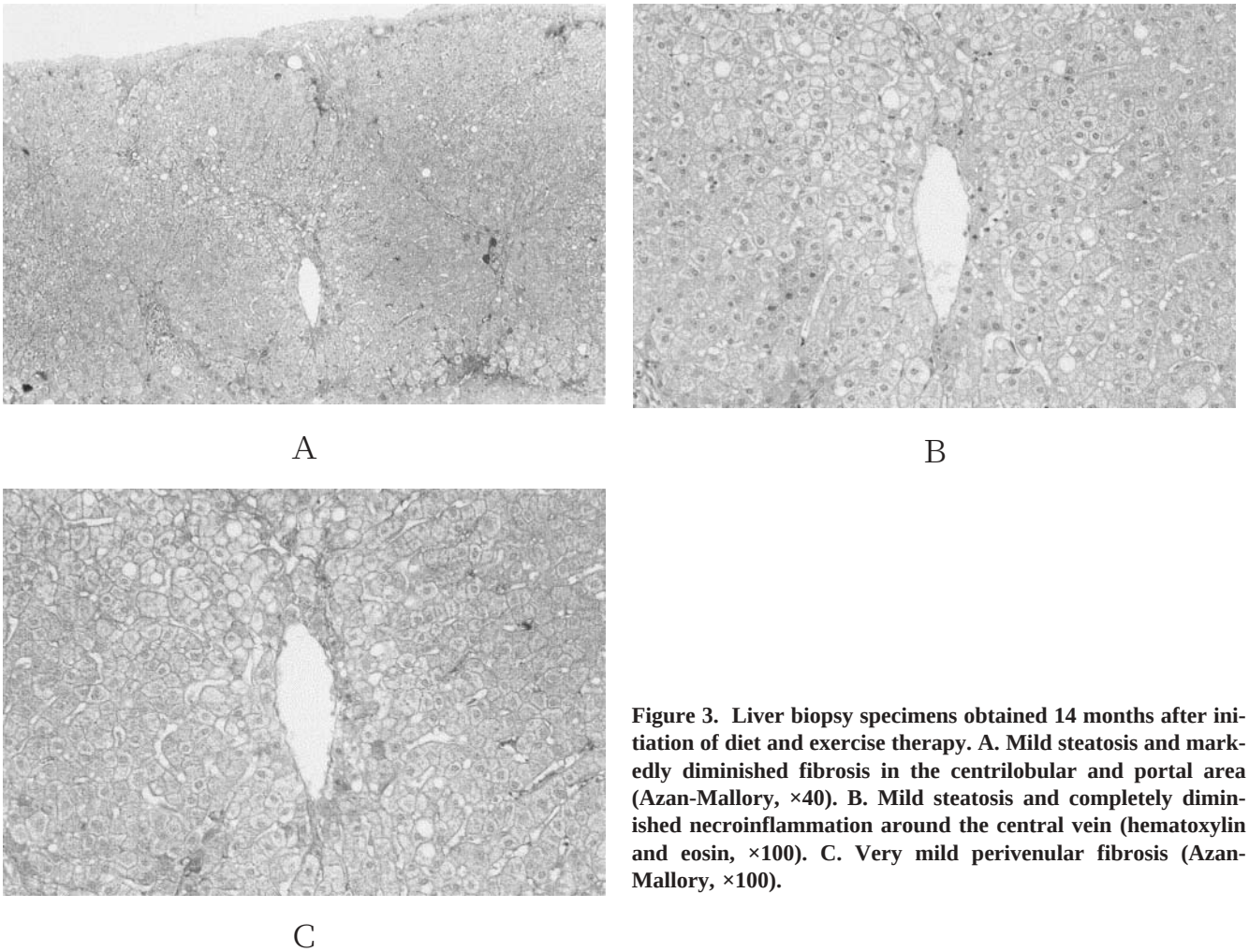

Figure 3. Liver biopsy specimens obtained 14 months after initiation of diet and exercise therapy. A. Mild steatosis and markedly diminished fibrosis in the centrilobular and portal area (Azan-Mallory, ×40). B. Mild steatosis and completely diminished necroinflammation around the central vein (hematoxylin and eosin, ×100). C. Very mild perivenular fibrosis (Azan-Mallory, ×100).

tablishment of an effective therapeutic approach is awaited, we believe that gradual weight reduction might be a useful first step in NASH therapy.

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