CASE REPORT

Nonalcoholic Fatty Liver Disease Manifesting Esophageal Variceal Bleeding

Chia-Pei Tang[1], Yi-Shin Huang[1]*, Shyh-Haw Tsay[2], Full-Young Chang[1], Shou-Dong Lee[1]

[1]Division of Gastroenterology, Department of Medicine, and [2]Department of Pathology, Taipei Veterans General Hospital, and National Yang-Ming University School of Medicine, Taipei, Taiwan, R.O.C.

Nonalcoholic fatty liver disease (NAFLD) is a fatty liver disease occurring in patients without alcohol consumption. It includes a broad spectrum of liver disease, from fatty infiltration, inflammation and fibrosis, to cirrhosis, usually having obesity, hyperlipidemia, and diabetes mellitus as its etiology. NAFLD-related cirrhosis has rarely been reported in Taiwan. We herein report a 41-year-old male patient with nonalcoholic fatty liver cirrhosis (NAFLC), with the first clinical manifestation being bleeding esophageal varices (EV). The patient was obese with diabetes mellitus, but without hyperlipidemia or any history of drinking alcohol. The laboratory tests, abdominal sonography, and computed tomography revealed a typical case of liver cirrhosis. The pan-endoscopy disclosed EV with red-color sign. EV ligation was performed successfully to stop the bleeding. When the patient was in a stabilized clinical condition, a liver biopsy showed a typical histologic finding of NAFLD. Most of the cases of NAFLC reported in the literature have silent signs and symptoms. Sudden onset of the EV as the first clinical manifestation, as in this case, is rare. This case reminds us that NAFLD may indeed induce severe liver impairment, such as liver cirrhosis. Liver biochemical tests and abdominal sonography should be considered in patients with overt obesity and diabetes. [*J Chin Med Assoc* 2006;69(4):175–178]

Key Words: diabetes mellitus, esophageal varices, nonalcoholic fatty liver cirrhosis, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, obesity

Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as fat accumulation in the liver exceeding 5–10% of total liver weight in nonalcohol users.[1] It comprises a wide variety of histologic findings, from steatosis, inflammation, hepatocyte ballooning and sinusoidal fibrosis, to polymorphonuclear cell infiltrates with or without Mallory hyaline body. Causes of NAFLD are obesity, diabetes mellitus (DM), hyperlipidemia, drugs, parenteral nutrition, gastric bypass surgery, and inherited metabolic disorders.[2] In Western countries, 20–30% of adults have excess fat accumulation in the liver.[1] It may progress to fibrosis, cirrhosis, and hepatocellular carcinoma.[3] NAFLD is common in Taiwan and this disease is usually considered benign without crucial clinical significance.[4] NAFLD-related cirrhosis has rarely been reported in Taiwan. We herein report an obese patient with type 2 DM who had nonalcoholic fatty liver cirrhosis (NAFLC) with bleeding esophageal varices (EV) as the first clinical manifestation.

Case Report

A 41-year-old male was brought to our emergency department because of hematemesis and passage of tarry stool for 1 day. He had no history of hepatitis, alcohol drinking, blood transfusion, chemical solvent

*Correspondence to: Dr. Yi-Shin Huang, Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, R.O.C.
E-mail: yshuang@vghtpe.gov.tw • Received: July 21, 2005 • Accepted: December 19, 2005

exposure, drug abuse, or herbal medicine intake. He had type 2 DM, having been treated with glucophage and glimepiride for 4 years, and had blood glucose levels controlled in an acceptable range. He weighed 102.5 kg and had a body height of 175.5 cm; thus, the body mass index (BMI) was 33.3 kg/m^2. In recent years, his serum transferase levels were found to reach 1–2 times the upper limit of normal range. On physical examination, the patient appeared robust and in acute distress. Lungs, heart, abdomen, arms, and legs were unremarkable. Mild palmar erythema was noted. However, there was no evident spider angioma, gynecomastia, or ascites.

On admission, his serum levels were as follows: alanine aminotransferase (ALT), 48 U/L (normal, 0–40 U/L); aspartate aminotransferase (AST) 48 U/L (normal, 5–45 U/L); total bilirubin 1.0 mg/dL (normal, 0.2–1.6 mg/dL); alkaline phosphatase 70 U/L (normal, 30–70 U/L); gamma-glutamyl transpeptidase 110 (normal, 8–60 U/L); albumin 3.7 g/dL (normal, 3.7–5.3 g/dL); globulin 2.4 g/dL (normal, 2.7–3.1 g/dL); cholesterol 167 mg/dL (normal, 125–240 mg/dL); triglyceride 75 mg/dL (normal, 20–200 mg/dL); high-density lipoprotein 79 mg/dL (normal, 30–70 mg/dL); low-density lipoprotein 97 mg/dL (normal, < 160 mg/dL); prothrombin time 13.9 seconds, fasting glucose 153 mg/dL (normal, 65–115 mg/dL); 2 hours post-prandial glucose 179 mg/dL (normal, <140 mg/dL); and HbA_{1c} 6.0% (normal, 4.5–6.2%). His fasting serum cortisol, free T4, and thyroid-stimulating hormone were in the normal range. The blood white cell count was 2,900/mm^3, hemoglobin 10.6 g/dL, and platelet 76,000/mm^3. Viral hepatitis markers were all negative, including hepatitis B surface antigen, anti-hepatitis C antibody, anti-Epstein Barr virus immunoglobulin M (IgM), anti-cytomegalovirus IgM, and anti-herpes simplex virus IgM. Hepatitis B virus DNA (Amplicor HBV Monitor Test, Roche Diagnostics, Pleasanton, CA, USA; sensitivity 1,000 copies/mL) and hepatitis C virus RNA (Amplicor HCV Monitor Test, Roche Diagnostics; sensitivity 600 IU/mL) were undetectable. The immunologic tests, including antinuclear antibody, anti-smooth muscle antibody, and anti-mitochondrial antibody, were all negative. His serum ferritin and ceruloplasmin levels were in the normal range of 115 ng/mL (normal, 38–280 ng/dL) and 31.9 mg/dL (normal, 22–58 mg/dL), respectively. An emergency pan-endoscopy examination was then done and revealed 4 EV (3F1 and 1F2) with positive red-color sign and portal hypertensive gastropathy. EV ligation (EVL) was effective.

Both computed tomography and abdominal sonogram revealed a typical fatty liver, an uneven surface of the liver, collateral circulation, and splenomegaly. A liver needle biopsy was performed, which disclosed liver cirrhosis (F4), mild activity (A1), and moderate fatty change (Figure 1). The mild activity (A1) meant mild inflammation (necrosis or inflammation cell infiltration in focal lobular area, or limited to the portal area only). The pathologic findings showed the typical findings of NAFLC: Mallory's body, sinusoidal and pericellular fibrosis, neutrophilic infiltration, macrovesicular fatty changes, septal fibrosis, and regeneration nodules. Furthermore, the immunohistochemical stain for hepatitis B core antigen was negative in the liver specimen. The patient was discharged uneventfully 14 days later.

Discussion

The patient presented here had type 2 DM and overt obesity. The World Health Organization has defined a BMI 25.0–29.9 kg/m^2 as class I obesity and a BMI higher than 30.0 kg/m^2 as class II obesity for people in the Asia-Pacific region.[5] Accordingly, 24% (20.2% of class I obesity and 3.8% of class II obesity) of adults are overweight in Taiwan.[4] Male sex, obesity, hypertriglyceridemia, and hyperglycemia are factors leading to fatty liver.[4] The prevalence of fatty liver and type 2 DM in the Taiwanese population is 36.9%[6] and 13.4 %[4], respectively. NAFLD is reported to be present in 20–25% of obese patients, whereas 2–3% have cirrhosis in Western counties.[7] In addition, old age, obesity, and diabetes predict liver fibrosis in NAFLD.[1] Our patient had 2 risk factors: obesity and diabetes.

In Farrell's study, less than 2% of NAFLD is drug related.[8] The drugs well-known to induce NAFLD are amiodarone, tamoxifen, and methotrexate.[8] However, the present case showed no such drug exposure history. Some surgical procedures, including gastroplexy, jejunoileal bypass, extensive small bowel resection, and bilio-pancreatic diversion, may also result in NAFLD.[3] Our patient previously had none of these procedures.

The majority of NAFLD patients are asymptomatic, even at the stage of cirrhosis. Nevertheless, malaise, fatigue, and right upper abdominal quadrant discomfort, due to distension of the Glisson capsule, may drive them to seek medical aid.[9] Mild elevation of serum transferase levels is one of the abnormal laboratory tests in NAFLD patients.[10,11] Usually, the

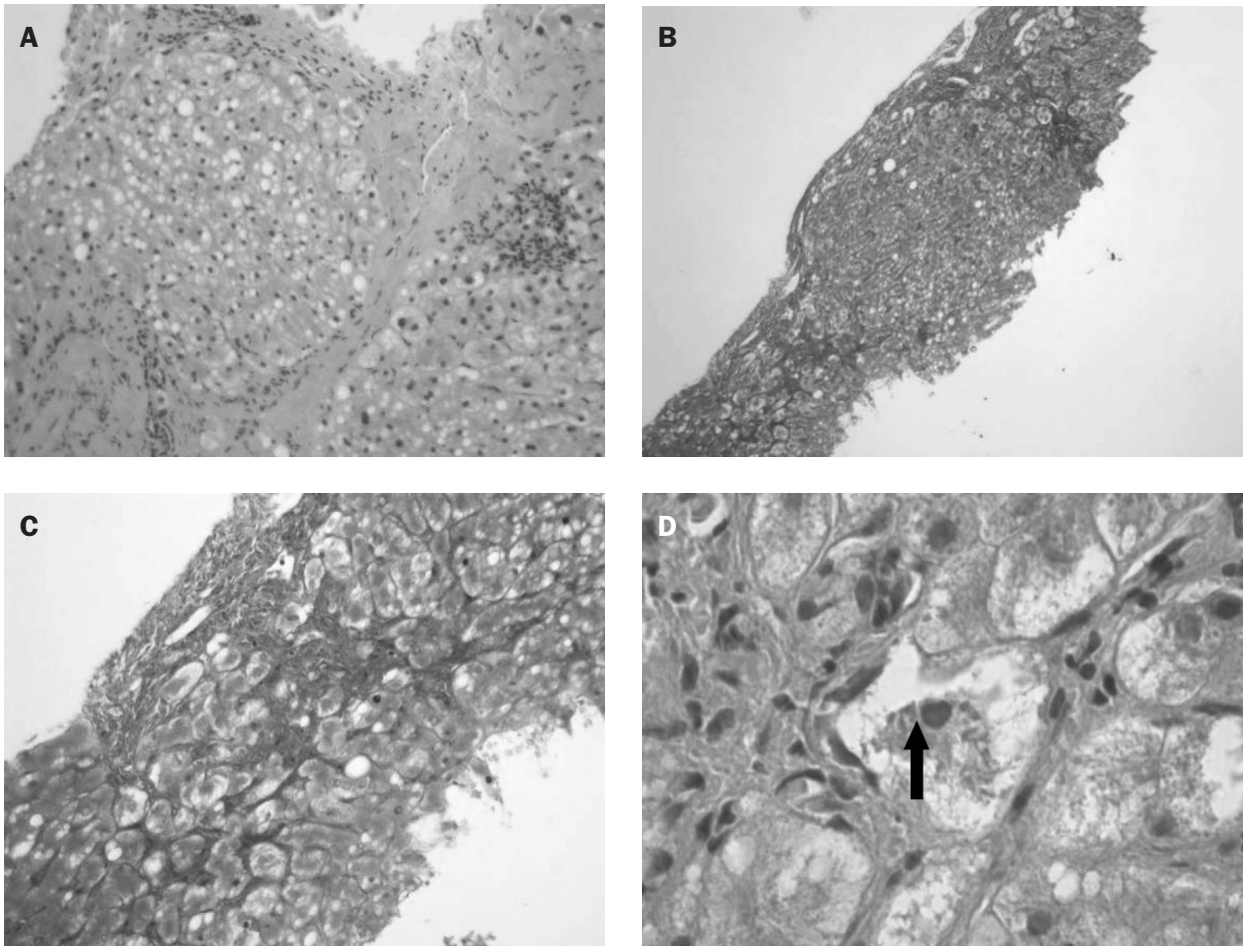

Figure 1. (A) Neutrophilic infiltration, ballooned hepatocytes, macrovesicular fatty change, and septal fibrosis (hematoxylin and eosin, × 400). (B) Steatohepatitis with cirrhosis characterized by fibrotic bands around the regeneration nodule and cytoplasmic macrovesicle fats (Masson trichrome, × 400). (C) Sinusoidal and pericellular fibrosis (Masson trichrome, × 1,600). (D) Mallory's bodies (arrow; hematoxylin and eosin, × 1,600).

serum ALT level is higher than the AST level. When the AST/ALT ratio goes beyond 1, liver fibrosis or cirrhosis should be suspected.[12] In our patient, the AST/ALT ratio was 1, which contributed little to the diagnosis of liver cirrhosis.

The diagnosis of NAFLD is established by exclusion of other possible liver diseases. Liver biopsy has been the gold standard for diagnosis. Brunt et al[13] proposed a pathologic classification of NAFLD from grade 1 (simple steatosis) to 4 (Mallory's hyaline or fibrosis with portal inflammation). The prevalence of cirrhosis is predominant in grades 3 and 4.[14] Inflammation in NAFLD is usually lobular, low grade, and with mixed neutrophil and mononuclear cell infiltration. The liver biopsy of our patient showed liver cirrhosis, severe fibrosis, portal inflammation, Mallory's body, and moderate fatty change (Figure 1). These pathologic findings were classified into grade 4.

The treatment of NAFLD is primarily to eliminate or modulate risk factors. It includes body weight control, adequate glycemic control in diabetic patients, treatment of dyslipidemia, and discontinuation of hepatotoxic medications. Weight reduction has proven effective to improve liver histology and serum aminotransferase in obese NAFLD patients.[15] Our patient was taught body weight reduction and normalized glycemic control upon discharge.

With the increasing prevalence of obesity and DM in Taiwan, numbers of patients with NAFLD are expected to grow. NAFLD is usually thought to be harmless and of little clinical significance. However, this case reminds us that NAFLD can evolve into severe liver disease, such as liver cirrhosis. Although NAFLD with the first clinical manifestation of EV bleeding, as in our patient, is rare, the mortality rate of EV bleeding is high. Therefore, proper liver function

tests, blood cell counts, and abdominal sonography surveillance are suggested in patients with morbid obesity and long-term poorly controlled DM. Once the AST/ALT ratio exceeds 1 or thrombocytopenia or leucopenia is noted, pan-endoscopy examination is recommended. If a large varix with red-color sign is found, prophylactic EVL or administration of beta-blockers may be considered to prevent EV bleeding.

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