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CASE REPORT

Histological Resolution of Steatohepatitis After Iron Depletion

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After its description in the early eighties (1), nonalcoholic steatohepatitis (NASH) has become a well-defined clinical entity with potentially dangerous consequences including progression to cirrhosis (2). The pathogenesis of NASH considers the occurrence of fat accumulation in the liver cell followed by a sequential series of events including an inflammatory response leading to hepatocellular injury which may lead to a fibrogenic response (3). While fat accumulation has been mainly related to insulin resistance, factors that trigger inflammation and fibrosis progression are less clear. Iron overload has been regarded as an important factor related to both insulin resistance and oxidative stress (4, 5). In fact, it has been reported that patients with hepatic steatosis have increased ferritin and transferrin saturation reflecting iron overload (6) and that iron depletion may have an insulin-sparing effect (7), which suggests a significant role of iron in the pathogenesis of fatty liver and NASH. Albeit it has been suggested that phlebotomy might be a useful treatment for NASH with concomitant iron overload, published data on the effects of iron depletion on both biochemical and histological alterations in these patients are limited.

In the present communication we report a patient showing complete histological resolution of NASH after iron depletion therapy, highlighting the importance of iron overload in the occurrence of both liver fat accumulation and inflammatory changes seen in NASH.

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CASE REPORT

A 53-year-old nonobese woman with beta thalassemia minor and porphyria cutanea tarda presented to our gastroenterology clinic due to asymptomatic elevation of aminotransferases. She had a long-standing history of mild microcitic anemia and blistering cutaneous lesions in sun-exposed areas. A cholecystectomy was performed 25 years ago. Hemoglobin electrophoresis was consistent with beta thalassemia and she had elevated urinary uroporphyrin and coproporphyrin levels (575 and 970.7 μg/24 hr, respectively). Laboratory studies showed the following: fasting glucose, 81 mg/dl (normal value [NV], 70 to 105); aspartate aminotransferase, 42 U/L (NV, <25); alanine aminotransferase, 68 U/L (NV, <30); alkaline phosphatase, 77 U/L (NV, <100); γ-glutamyl transpeptidase, 112 U/L (NV, <50); total bilirrubin, 0.77 mg/dl; conjugated bilirrubin, 0.22 mg/dl; prothrombin time (INR), 1; ferritin, 762 ng/ml (NV, <417); and transferrin saturation, 70%. Antibodies against hepatitis C virus, hepatitis B surface antigen, hepatitis B total anticore antibodies, antinuclear, and anti-smooth muscle antibodies were all negative, while an abdominal ultrasound revealed diffuse liver hyperechogenicity and intrahepatic lithiasis with segmentary left bile duct dilatation. These findings were later confirmed by a magnetic resonance cholangiography.

A percutaneous liver biopsy showed significant fatty infiltration (20% of hepatocytes), mild inflammatory infiltrate, hepatocyte ballooning in zone 3, and mild pericellular and perisinusoidal fibrosis (Figure 1a). Marked siderosis of central and middle lobular hepatocytes was noted using the Pearl's stain. Genetic analysis of the HFE gene revealed the presence of heterocygocity for the H63D mutation and no C282Y mutation.

The patient underwent six phlebotomies every 2 weeks, resulting in clinical improvement of cutaneous lesions and reduction of urinary porphyrin metabolite excretion, serum iron, ferritin, and aminotransferases to normal levels after six venesections of 500 ml each (Figure 2).

Three months later, the patient underwent a left subsegmentary liver resection for resolution of hepatolithiasis, confirming the presence of multiple left intrahepatic bile stones. A repeated liver biopsy was obtained during surgery. Histological examination revealed complete resolution of fatty infiltration and inflammatory changes (Figure 1b). In addition, there was no histological evidence of fibrosis or iron accumulation using

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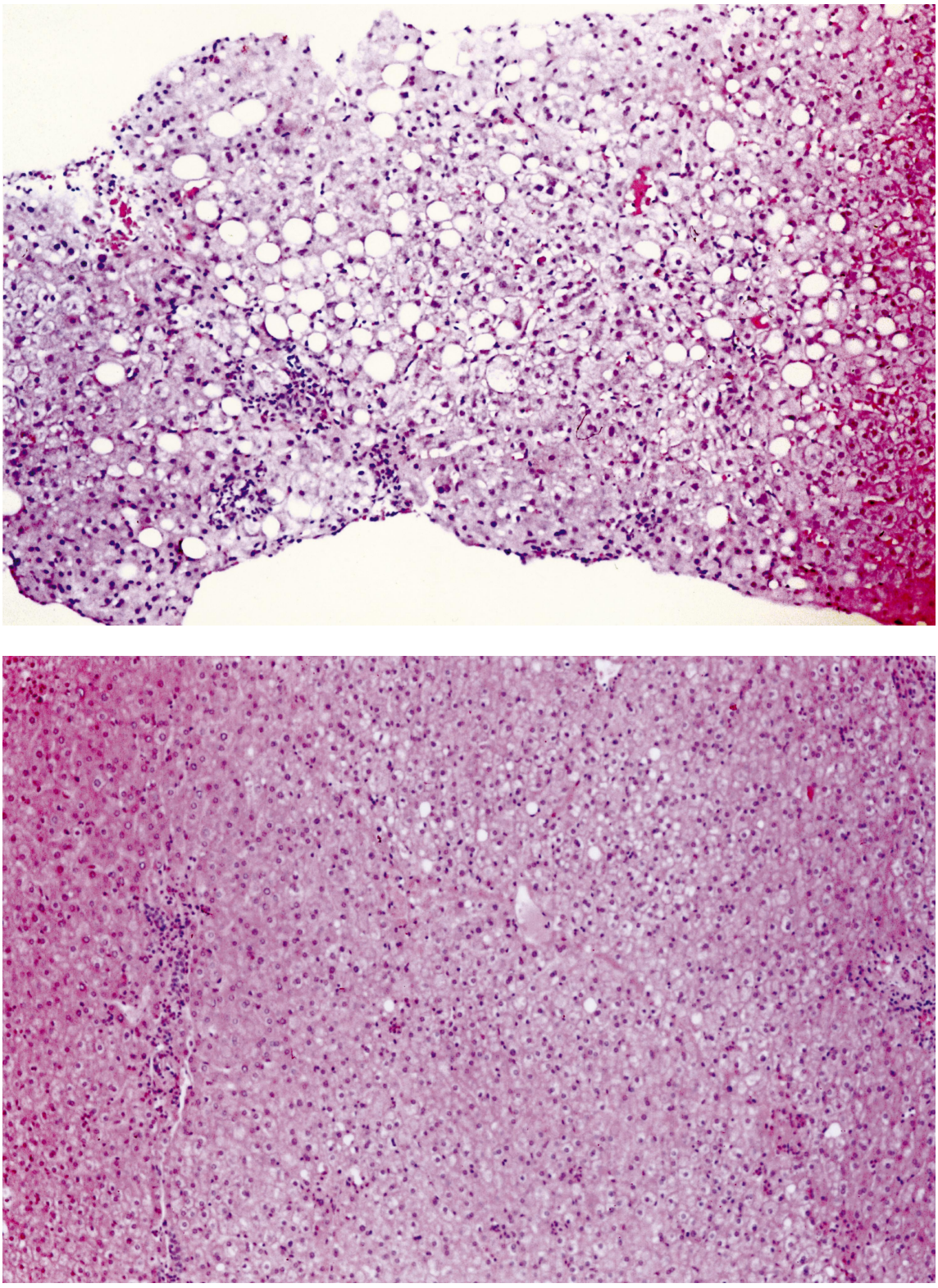

Fig 1. Liver histology before (a) and after (b) phlebotomies in a patient with nonalcoholic steatohepatitis and porphyria cutanea tarda-associated iron overload. Complete histological resolution of both fatty infiltration and inflammatory changes was observed after six venesections.

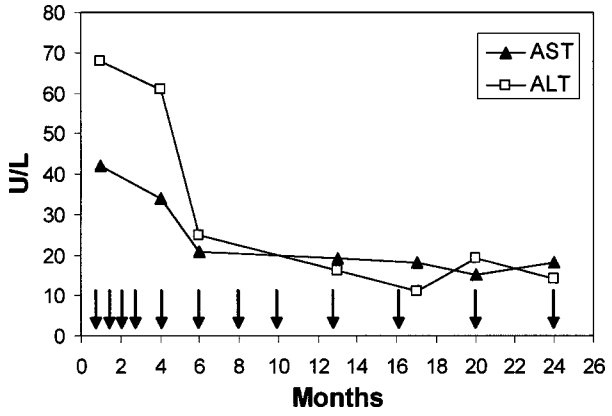

Fig 2. Temporal evolution of aminotransferase levels, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Venesections are indicated by arrows.

Pearl's stain. The patient's weight remained stable throughout this period.

DISCUSSION

Liver steatosis and steatohepatitis are extremely prevalent conditions in the general population, with an average prevalence of 20% for NAFLD and 2–3% for NASH (8). The potential of this disease for progression to cirrhosis, decompensation, and even hepatocellular carcinoma is now well described (9–11). Risk factors associated with progression of fibrosis in NASH include obesity, type 2 diabetes mellitus, and older age (12).

NAFLD is commonly viewed as a two-stage process in which insulin resistance leads to steatosis in hepatocytes ("first hit") (3). Several different mechanisms have been implicated as the elusive "second hit." Both clinical and experimental data suggest that increased oxidative stress is common to these mechanisms. Oxidative stress may arise from steatosis per se (13), decreased levels of antioxidants (14), action of cytokines in the liver (15), increased activity of mitochondrial uncoupling proteins (16), increased activity of cytochrome P450 2E1 (17), and increased iron stores. Iron overload has been regarded as an important factor related to both insulin resistance and oxidative stress. Since iron promotes oxidative stress in the liver, it is a good candidate as a contributory factor in the pathogenesis of NASH. Products of lipid peroxidation induced by iron include malondialdehyde and 4-hydroxynonenal, which have been shown to activate hepatic stellate cells in vitro (18) and increase collagen production by stellate cells (19). The relationships among iron, insulin resistance, and NAFLD are complex and remain incompletely understood at this time (4).

Some studies, especially early reports, showed a high prevalence of abnormally elevated serum markers of iron overload (20). Another study showed histological evidence of iron overload in these patients and raised the question of iron as potentially linked to liver injury (6). This was attributed to a higher prevalence of HFE gene mutations C282Y and H63D among these patients. Intensity of iron overload correlated with liver fibrosis. Nevertheless, all these patients had mild to moderate iron overload and normal hepatic iron index. Other studies have failed to show a clear association between iron overload and NAFLD severity (fibrosis) (12, 21, 22). Therefore, although serum markers of iron overload are frequent in NAFLD, measured liver iron is normal or only slightly elevated in these patients and its association with the severity of liver fibrosis is unclear.

In a recent and provocative study conducted in patients with carbohydrate intolerance and clinical evidence of NAFLD (23), phlebotomy was performed with the intention of iron depletion, with histological evidence of improvement. We believe that this report serves as proof of the concept that iron depletion can be followed by significant improvement or normalization of biochemical and histological features of NASH (23, 24). However, prospective studies are required to assess the role of iron depletion in the management of NASH before this can be advocated as a therapeutic option.

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