

CLINICAL VIGNETTE

Cirrhosis Secondary to Nonalcoholic Fatty Liver Disease

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Introduction

Primary care physicians often encounter incidental transaminitis or fatty liver on abdominal imaging. A common cause of this is Nonalcoholic Fatty Liver Disease (NAFLD), especially in those with metabolic syndrome. Given how commonly primary care physicians encounter this, and misconceptions surrounding diagnosis and treatment, we review a patient with NAFLD.

Case Report

An 83-year-old obese, Hispanic female with history of multiple medical problems including Type II Diabetes with nephropathy, hyperlipidemia, and hypertension presented to the clinic to establish care. She had recently moved to the United States from Chile, and upon review of her old medical records, she had an elevated total bilirubin (TB), alkaline phosphatase (ALP), Aspartate aminotransferase (AST), and Alanine aminotransferase (ALT) in September 2014. The patient was aware of the abnormal labs but was not given a diagnosis. No further workup was pursued. Her current physical exam was only remarkable for morbid obesity and bilateral lower extremity edema. Repeat liver function tests revealed only a minor isolated elevation in the AST. She also had mild thrombocytopenia, and LFT's two weeks later showed mild elevations in TB and AST. The thrombocytopenia resolved and was felt secondary to either a viral infection versus polypharmacy versus idiopathic thrombocytopenic purpura. Suspicion for NAFLD was high, with obesity, Type II Diabetes, hyperlipidemia, and thrombocytopenia. Additional labs included: AST: ALT ratio ≤ 2 , and normal serum alcohol, PT, PTT, iron, celiac disease panel, ANA, CK, and INR. Viral hepatitis panel showed immunity to Hepatitis A and negative HepB and HepC. A BNP was mildly elevated; however, it was thought to be falsely positive given obesity and CKD with the stress echo within normal limits. Abdominal ultrasound showed mild hepatomegaly with normal echogenicity but subtle nodularity suggestive of early cirrhosis, as well as mild splenomegaly. She was seen by hepatology who raised concerns about cardiac cirrhosis secondary to right heart failure secondary to pulmonary hypertension. However, a transthoracic ECHO was within normal limits, and the patient was felt to have NAFLD. Upper endoscopy showed small esophageal varices, and the patient will be followed by Hepatology for early cirrhosis secondary to Nonalcoholic Steatohepatitis (NASH).

Discussion

Nonalcoholic Fatty Liver Disease, or hepatic steatosis, is subdivided into Nonalcoholic Fatty Liver (NAFL) and Nonalcoholic Steatohepatitis (NASH) after other causes have been excluded. NAFL is hepatic steatosis without inflammation. NASH is hepatic steatosis with inflammation, which results in an increased risk for cirrhosis, and subsequently, hepatocellular carcinoma.¹ The actual rate of progression from NAFL to NASH to advanced fibrosis to cirrhosis has varied amongst several studies with hepatic inflammation on biopsy the biggest risk factor for disease progression. Thus, NAFL has the lowest risk of progression, and NASH the highest risk of progression to advanced liver disease.² In a systematic review, those without cirrhosis had a 0 to 3% chance of progression to hepatocellular carcinoma, and those with cirrhosis had a 2.4% risk over 7 years and 12.3% risk over 3 years, which is still less than those with Hepatitis C cirrhosis.³

Studies report high prevalence of NAFLD with a median of 20% worldwide. United States studies report prevalence from 10-46%, most commonly in the fourth to sixth decades. NAFLD has higher prevalence in Mexican Americans, those with diabetes and obesity. There is a lower prevalence in non-Hispanic blacks, Alaskan-Native and American-Indian populations, although the latter two may be underestimated given lack of histologic evidence. NASH, specifically, has a prevalence of approximately 3-5%, and the prevalence of NASH cirrhosis is undetermined.^{3,4} In diabetics, the prevalence of NAFLD has been reported to be as high as 70-80%. Obese patients undergoing bariatric surgery have prevalence of NAFLD reported as high as 90%, with 5% having undetected cirrhosis.³ Other risk factors include pre-diabetes, hypertension, and hyperlipidemia (mostly hypertriglyceridemia and low HDL, with a NAFLD prevalence of 50%), obstructive sleep apnea, history of cholecystectomy, polycystic ovarian syndrome, hypothyroidism, hypopituitarism, hypogonadism, total parenteral nutrition, and possibly a genetic predisposition. A proposed independent risk factor is cardiovascular disease, but the largest study conducted did not control for hyperlipidemia and hypertension, which in themselves are risk factors for cardiovascular disease.^{3,4} As mentioned previously, hepatic inflammation, and therefore NASH, is the biggest risk factor for progression to advanced disease. However, other risk factors include older age, diabetes, elevated serum aminotransferases, BMI ≥ 28 , high visceral adipose tissue

(measured by waist circumference, BMI, triglycerides, and HDL), and heavy episodic alcohol consumption, which has varied definitions, but overall is defined as >21 drinks per week in men and >14 drinks per week in women over a 2-year period prior to baseline liver histology.³

Cardiovascular disease is the most common cause of death in those with NAFLD. Several smaller studies have confirmed this; however, the largest study in the United States showed there was no difference in overall mortality compared to the general population.⁵

The etiology of NAFLD is unclear, but the most widely accepted theory involves insulin resistance. It is theorized that a combination of multiple factors (obesity, diet, activity levels, genetics, and environment) cause increased lipolysis resulting in high levels of free fatty acids [FFA] (also from decreased hepatic export, and impaired beta-oxidation of free fatty acids) leading to decreased glucose clearance and increased glucose production, leading to hyperinsulinemia, and then the cycle repeats. Subsequently the increase in FFA leads to triglyceride accumulation, resulting in hepatic steatosis.^{1,4}

Most patients with NAFLD are asymptomatic. However, they may present with generalized fatigue, malaise, and right upper quadrant pain. The physical exam is also often normal but can present with hepatomegaly or signs of cirrhosis.¹

Because patients are usually asymptomatic and have a normal physical exam, the diagnosis is often made when a patient is incidentally found to have abnormal liver function tests. Alternatively, fatty liver is an incidental finding on abdominal ultrasound or other imaging modalities. Asymptomatic patients with normal liver function tests incidentally found to have hepatic steatosis are evaluated for metabolic risk factors and other causes of hepatic steatosis, but liver biopsies are not recommended. If symptomatic or abnormal liver function tests, and incidentally found to have hepatic steatosis on imaging, proceed with NAFLD work up. In order to diagnose NAFLD, the patient must meet all four of the following criteria: hepatic steatosis via imaging or biopsy, exclusion of alcohol abuse, exclusion of other causes of hepatic steatosis, and no co-existing causes for chronic liver disease.³

Lab abnormalities can include the following: Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) elevations two to five times the upper limit of normal, with an AST:ALT <1, although it is not a requirement for diagnosis and the degree of elevation does not correlate with the severity or presence or absence of histologic changes; Alkaline phosphatase (ALP) may be two to three times the upper limit of normal. If the patient has developed cirrhosis, he or she may present with elevated bilirubin and albumin levels, prolonged prothrombin (PT) time, neutropenia, and thrombocytopenia.⁵ Mildly elevated serum ferritin levels can be seen in NAFLD and does not necessarily mean increased iron stores; however, when 1.5 times the upper limit of normal, along with elevated transferrin saturation, this correlated with greater risk of hepatic fibrosis. Thus, genetic testing for homozygote or compound heterozygote C282Y mutation, specifically, in the HFE gene should be considered, given non-specific HFE gene mutations do occur in NAFLD

patients with unclear significance. If suspicion for NAFLD is high, the patient has significantly elevated serum ferritin levels, and has the previously mentioned specific genetic mutation, a liver biopsy should be considered.³ The significance of positive serum autoantibody titers is not clear as it is commonly seen in patients with NAFLD (ANA > 1:160 or ASMA >1:40 in 21% according to one study) with no relationship to severity of histology.^{3,5} However, if significantly elevated and there is concern for autoimmune liver disease (significantly elevated aminotransferases, high globulin levels), proceed with further work up.³

The diagnosis of NAFLD requires exclusion of other causes of hepatic steatosis. These include:

- Alcoholic Liver Disease
- Hepatitis C (particularly genotype 3)
- Wilson disease
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Gastric Bypass
- Surgery
- Abetalipoproteinemia
- Medications (amiodarone, methotrexate, tamoxifen, glucocorticoids, valproate, anti-retroviral agents for HIV)
- Reye's syndrome
- Acute fatty liver of pregnancy
- HELLP (hemolytic anemia, elevated liver enzymes, low platelet count) syndrome
- Inborn errors of metabolism (LCAT deficiency, cholesterol ester storage disease, Wolman disease)
- Thyroid disease
- Celiac's Disease
- Alpha-1 antitrypsin deficiency
- Budd-Chiari Syndrome

If the patient has steatosis and steatohepatitis but also has other chronic liver disease, assess metabolic risk factors and other causes for steatosis.³

Thus, the initial work up should always include the following: anti-Hepatitis A IgM, Hepatitis BsAg, BsAb, BcAb, anti-hepatitis C antibody, plasma iron, total iron binding capacity, and ferritin; one may consider serum gammaglobulin levels, ANA, antismooth muscle antibody, and anti-liver/kidney microsomal antibody-1 levels. It is currently not recommended to screen patients for NAFLD or screen patients with a family history of NAFLD given lack of evidence regarding diagnosis, treatment, long-term benefits, and cost-effectiveness of screening.³

Liver biopsy is the gold standard for diagnosis as it has the ability to distinguish between NAFL and NASH (not distinguish NASH from alcoholic steatohepatitis) and predict severity, which imaging cannot. However, NAFLD can also be diagnosed based off imaging studies alone if the following criteria are met:

- Radiographic imaging (US, CT, or MRI) is consistent with fatty infiltration;
- Other causes for the patient's liver disease have been excluded;
- The patient does not have signs or symptoms of cirrhosis; and
- The patient is not at high risk for advanced fibrosis or cirrhosis.

If the diagnosis is still unclear, a liver biopsy may be considered. There is no consensus on who should get a liver biopsy and repeating liver biopsies in those with NAFLD is not recommended.^{3,6} However, it should be considered in patients who meet the criteria below, as a definitive diagnosis can guide management or encourage lifestyle changes:⁵

- Peripheral stigmata of chronic liver disease (suggestive of cirrhosis);
- Has splenomegaly (suggestive of cirrhosis);
- Has cytopenias (suggestive of cirrhosis);
- Has a serum ferritin >1.5 times the upper limit of normal (suggestive of NASH and advanced fibrosis); and
- Increased risk of NASH and advanced fibrosis: >45 years of age with associated obesity or diabetes, NAFLD fibrosis score >0.676, excluded other diagnoses of hepatic steatosis, during bariatric surgery, during cholecystectomy.⁴

Of note, the NAFLD fibrosis score (NFS) uses six variables that are independent indicators for advanced fibrosis (age, hyperglycemia, body mass index, platelet count, albumin, and AST/ALT ratio) and has a high negative predictive value; thus, using this score may help avoid a significant number of liver biopsies.⁶

The NAFLD Activity Score (NAS) is a method of grading disease severity based on histology after a liver biopsy with a score of < 3 representing NAFL and score of ≥ 5 representing NASH.⁷

The other non-invasive methods for detecting advanced fibrosis, such as transient elastography, AST:Platelet ratio index, and serum cytokeratin-18 (CK-18) biomarker have not been extensively studied.³

A variety of treatments for NAFLD have been proposed, but there is limited evidence regarding their effectiveness. In 2012, the American Association for the Study of Liver Diseases (AASLD), the American Gastroenterology Association (AGA), and the American College of Gastroenterology (ACG) released practice guidelines for management of NAFLD, and in 2014, the World Gastroenterology Organization (WGO) also released very similar practice guidelines. The mainstay is treatment of the metabolic syndrome: diet and exercise for weight loss, treatment of diabetes and hyperlipidemia, and abstinence from alcohol. Some studies suggest decreasing fructose intake may help given it has a high glycemic index and can be converted to triglycerides; also, it is suggested that two to three cups of caffeinated coffee per day may reduce the risk of fibrosis in those with NASH.^{3,4,8} For NAFL, there is no liver-specific

treatment as there is for NASH. A discussion of the evidence behind various treatments is below:

Weight Loss: Overall, weight loss in overweight or obese patients has been shown to improve liver histology and is the only treatment with reasonable evidence; however, its main benefit is cardiovascular risk modification and at least 3% body weight loss (10% for improvement in hepatic inflammation) of no greater than 0.5-1 kg/week (1 to 2 lb/week) is recommended, as rapid weight loss tends to increase one's risk of portal fibrosis for unclear reasons.^{3,4} Primarily, diet (25% reduction in caloric intake) alone or in conjunction with exercise (3-4 times per week, for 45 minutes each session) are recommended.^{3,8} Exercise alone can result in improvement in hepatic steatosis, but it is unclear how it affects other types of histology.³ If this fails after a 6 month period, weight loss medications and bariatric surgery may be considered. The most common weight loss medications recommended are: Qsymia (phentermine/topiramate), which can result in up to 15% weight loss; Contrave (bupropion/naltrexone), which can result in up to 7% weight loss; and Belviq (lorcaserin), which can result in up to 5% weight loss. Orlistat is not recommended because of conflicting studies regarding its effectiveness.^{3,4,8} These drug studies were short-term and focus more on improvement in liver enzymes and histology with conflicting results, rather than larger outcomes, such as decompensated cirrhosis, and thus are not recommended solely for the treatment of NASH.³ Bariatric surgery (gastric banding with slightly better outcomes than roux-en-y gastric bypass) should be considered if the patient does not have cirrhosis and has a BMI > 35 and obesity-related comorbidities, or a BMI > 40 and failed a trial of diet and exercise with or without medical treatment. However, given surgery can worsen fibrosis, liver function should continue to be monitored closely.⁴ This can result in improvement of metabolic syndrome, lab values, and histology (91% of the time), but overall, at this time, it cannot be recommended to specifically treat NASH.^{3,4}

Diabetes Management: Thiazolidinediones, of which not all have equal anti-diabetic effects, and specifically pioglitazone, can result in improvement in histology of biopsy-proven NASH, but most may not result in histologic improvement after the first year of treatment. All studies were conducted on non-diabetics, and length of treatment, efficacy, and risk of side effects (weight gain, myocardial infarction, congestive heart failure, osteoporosis, and bladder cancer, which has a 22% increased risk after use for ≥ 5 years) in non-diabetics. Those with NAFLD and coexisting other chronic liver disease is controversial.^{3,9} Thus, many specialists recommend this medicine should only be tried in diabetics. Metformin has no effect on liver histology, but it can be used in diabetics with NASH.⁴

Hyperlipidemia Management: Statins are primarily used to treat hyperlipidemia rather than NASH itself, given that despite improvement in liver enzymes and cardiovascular outcomes, there are no randomized controlled trials evaluating histologic changes. A statin can be continued in a patient with compensated cirrhosis.^{3,4}

Antioxidants: Vitamin E 800 IU per day can be considered as first line treatment for biopsy-proven NASH in non-diabetics without cardiovascular disease as it results in improvements in liver histology. It is not recommended in diabetics, NAFLD without liver biopsy, NAFLD with co-existing liver disease, or any type of cirrhosis until further studies are available. Moreover, greater than or equal to 400 IU per day may increase all-cause mortality, and usually 800 IU per day is required for improvement in liver histology. There is also a 21% increased risk of hemorrhagic stroke, an increased risk of prostate cancer after 3 years of use, and it takes years of daily supplementation before positive benefits may be seen. Ursodiol, which is an apoptotic or anti-inflammatory, showed no benefit in the largest studies, thus is not recommended for treatment of NAFLD. Although omega-3 fatty acids have shown to decrease steatosis in randomized control trials, at this time, it is not recommended to treat NAFLD specifically.⁴ There is variable evidence regarding pentoxifylline as there is a high dropout rate in many studies given the side effect of nausea.¹⁰ There is not enough evidence to recommend the use of Obeticholic acid, Armachol, Probuco, Betaine, and Losartan.¹¹

Liver transplant: In those patients with cirrhosis secondary to NAFLD, the criteria for liver transplant are similar to other patients with cirrhosis. There have been recurrences of NASH (2-4%) after liver transplant, but the studies regarding this are small.⁸

Overall, if labs and imaging are within normal limits and the patient does not have any risk factors for fibrosis or cirrhosis, or has a liver biopsy that is only positive for simple steatosis, and thus has NAFL, treatment suggested includes weight loss via exercise, medications mentioned previously, or surgery; treatment of diabetes; treatment of hyperlipidemia with statins or fibrates, although this has not shown to change the outcome. The patient should also receive Hepatitis A and B vaccines if not immune, as well as pneumonia, influenza, and Tdap vaccines. Abstinence from alcohol is best, although it is unclear whether light or moderate alcohol consumption is harmful or beneficial.^{3,4} Liver function tests and an abdominal ultrasound should be repeated in 6 to 12 months; if within normal limits, both should be repeated in 1 year. If the results are still within normal limits, frequency of repeat labs and imaging is at the discretion of the provider. If the results are not normal at either initial follow-up or subsequent follow-up, patient should be referred for biopsy. If the patient has NASH with either advanced fibrosis (Stage 3+) or most importantly, cirrhosis, they should have hepatocellular carcinoma screening via yearly AFP and abdominal ultrasound, as well as screening for esophageal varices. A liver biopsy can be repeated at 5-7 years if the initial biopsy was positive for NASH and the patient is stable; however, if it is worse, it can be repeated sooner. However, some studies do not support repeat liver biopsies in general.³⁻⁵ If the patient has steatohepatitis or cirrhosis on biopsy, a MELD score of greater than or equal to 10, or decompensated cirrhosis that may qualify them for liver transplant, refer to Hepatology.⁴

Conclusion

NAFLD, which is subdivided into NAFL (steatosis without inflammation) and NASH (steatosis with inflammation and thus increased risk for progression to advanced fibrosis and cirrhosis), affects approximately 20% of people worldwide, most prominently in the fourth to sixth decades, Mexican Americans, and those with diabetes and obesity. The etiology is unknown. The most significant risk factors encompass the metabolic syndrome, but screening in the general population is not recommended. It is often diagnosed incidentally after abnormal liver function enzymes and/or fatty liver on abdominal imaging. Liver biopsy is only recommended under certain circumstances. Benefits of different treatments are controversial given lack of consistent evidence, but it is initially geared towards weight loss through diet and exercise and abstinence from alcohol. If this fails, weight loss medications, bariatric surgery, treatment of underlying diabetes and hyperlipidemia, and use of some antioxidants, if able to accept the risk of side effects, is suggested. Timing of follow-up labs, imaging, hepatocellular cancer screening, and repeat liver biopsies depends on the initial diagnosis and current status of the patient. Areas of future research should be directed at more evidence regarding treatment options.

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