

Hepatic Steatosis Resulting From *LMNA*-Associated Familial Lipodystrophy

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent liver disease worldwide, with potential causes stemming from obesity, metabolic syndrome, genetic disorders, and drug toxicity. We report a 42-year-old woman with lipodystrophy and NAFLD due to a pathogenic variant in the *LMNA* (D300N) gene. This case report attempts to encourage clinicians to consider genetic diseases, specifically lipodystrophies, when working up uncommon causes of NAFLD.

INTRODUCTION

Steatosis of the liver is a pathological process resulting from a wide array of etiologies, including metabolic and nutritional disorders, alcohol, drug, or toxin ingestion, and infectious pathogens. Nonalcoholic fatty liver disease (NAFLD) refers to fatty liver that is not secondary to heavy alcohol consumption.¹ NAFLD is the most common liver disease worldwide, with obesity and type 2 diabetes serving as the main risk factors for developing NAFLD.² Genetically acquired metabolic diseases and certain toxins/drugs can also lead to NAFLD.¹ Although the literature is limited when quantifying the prevalence of NAFLD secondary to genetically acquired metabolic diseases, there are some data in twin studies to suggest that overall genetic factors could explain up to 60% of the variability in NAFLD.³ Clinical judgment to screen for more unusual causes of fatty liver disease depends on the recognition of patterns of disease that may set some disorders apart from most of the “classic” NAFLD. We report a patient with lipodystrophy and NAFLD due to a pathogenic variant in *LMNA* (D300N).

CASE REPORT

A 42-year woman presented for evaluation of abnormal liver imaging. Her medical history included hypertension, sleep apnea, Barrett’s esophagus, and pancreatitis. The patient also had a medical history of heart disease that includes severe symptomatic aortic stenosis, mitral regurgitation, tricuspid regurgitation, and congestive heart failure secondary to valvular heart disease. The patient underwent an aortic valve replacement and had nausea, vomiting, and multiple abdominal symptoms after the surgery. She was found to have pancreatitis with no evidence of gallbladder stones or pathology leading to pancreatitis. The episode resolved and was attributed to the open-heart surgery, and no biliary intervention was necessary. In the course of her testing, she underwent an abdominal ultrasound which demonstrated hepatic steatosis without evidence of cirrhosis. Her most recent liver chemistries showed a normal alanine aminotransferase of 33 U/L, aspartate aminotransferase of 26 U/L, alkaline phosphatase of 65 U/L, and albumin of 4.8 g/dL. Her most recent lipid panel showed elevated triglycerides of 353 mg/dL and a decreased high-density lipoprotein of 31 mg/dL with normal total cholesterol and a normal low-density lipoprotein. The patient had no history of alcohol consumption, hepatotoxic medication, or a family history of inherited liver disorders. Furthermore, she had a lean body habitus and face with well-defined trunk and extremity muscles. Her body mass index was 19 kg/m², and she had no personal history of obesity or dyslipidemia. Physical examination demonstrated normal liver span and contour with no stigmata of chronic liver disease. The patient’s family history was notable for a father with a history of valvular disease who was also quite thin.

Before consultation, the patient had undergone vibration-controlled transient elastography which found a controlled attenuation parameter of 286 dB/m and a liver stiffness score of 7.6 kPa. This indicated significant hepatic steatosis (controlled attenuation parameter indicated >66% steatosis) with stage 2 fibrosis. Given the patient's only risk factor at that time was elevated triglycerides, her degree of hepatic steatosis raised suspicion of an alternative underlying etiology. The patient's hepatologist was struck by the possibility of a congenital lipodystrophy, given the degree of steatosis with little observed fat reserves throughout her body. In addition, her father's and her history of valvular disease led to further consideration of a congenital etiology. Other potential etiologies such as hepatitis C, Wilson's disease, and celiac disease were not immediately pursued. This was because of a low clinical suspicion, given the isolated steatosis, normal current, historical liver chemistries, and the absence of additional symptoms or physical examination findings. Shortly after her hepatology appointment, the patient met with a geneticist who agreed to conduct the appropriate genetic testing. She underwent molecular testing with a lipodystrophy panel that revealed heterozygosity for a pathogenic D300N variant in the *LMNA* gene. This suggested a diagnosis of autosomal dominant familial partial lipodystrophy (FPLD) syndrome.

DISCUSSION

Affecting 14%-30% of the general population, NAFLD is the most common chronic liver disease and will likely be the leading indication for liver transplantation by 2020.^{1,4,5} Obesity, type II diabetes, dyslipidemia, and hypertension are the primary risk factors for NAFLD. For patients who present with NAFLD in the absence metabolic syndrome and other primary risk factors, it is important to consider the less common causes of NAFLD. Some of these less common causes include hepatitis C, drug-induced NAFLD, and celiac disease. In some rare instances, environmental toxins such as petroleum chemicals, *Bacillus cereus* toxin, and *Amanita phalloides* mushrooms have been linked to NAFLD.⁴ In addition, disorders of lipid metabolism including abetalipoproteinemia, hypobetalipoproteinemia, and lipodystrophies can also lead to NAFLD. A *LMNA* gene mutation with the D300N variant leading to FPLD was the likely cause of NAFLD in this patient.

The metabolic abnormalities associated with lipodystrophies include insulin resistance, hypertriglyceridemia, and hepatic steatosis, as we saw in this patient. The most common cause of hereditary lipodystrophy is a mutation in the *LMNA* gene. Other forms of lipodystrophy can be acquired; this includes acquired partial lipodystrophy, which is associated with autoantibody complement 3 nephritic factor. Drug-induced lipodystrophy can occur in patients with human immunodeficiency virus taking protease inhibitors or nucleoside analogs. Insulin injections, steroid injections, and other injectables can cause localized lipodystrophy.⁶

The *LMNA* gene codes for 2 major lamin proteins, lamin A and lamin C. Mutations in the *LMNA* gene are linked to multiple diseases, including, limb-girdle muscular dystrophy, Hutchinson-Gilford progeria syndrome, and FPLD. This patient's exon 5 mutation (D300N) is a semiconservative amino acid substitution affecting secondary protein structure, specifically the alpha-helical rod domain.⁷ To our knowledge, this is the first case D300N variant linked to clinical NAFLD. The *LMNA* gene is associated with cardiovascular disease, including valve calcification, cardiomyopathy, and accelerated atherosclerosis.^{8,9} Valvular disease was seen with this patient and her father. It may be important for clinicians to consider a diagnosis of lipodystrophy in patients presenting with idiopathic fatty liver and concomitant history of valvular disease. Although the wide variety of pathologies caused by *LMNA* gene mutations highlights the complexity of genetic testing and precision medicine, there is a clear benefit to bringing a comprehensive image of the patient's own health and providing clinicians with more tools to help patients.¹⁰ In the case of this patient, her *LMNA* gene mutation was approached from a multidisciplinary prospective. Although there was no acute intervention from the prospective of hepatology, she continues to be monitored longitudinally. In addition, endocrinology was consulted who subsequently decided to evaluate her serum leptin levels (normal at 3.6 ng/mL) and ordered a whole body DEXA scan to quantitate total and regional body fat. Her cardiologists were informed of her diagnosis, and they continue to follow her valvular disease and heart function.

This patient's mutation in the D300N variant in the *LMNA* gene causing NAFLD is unique because there is minimal literature about the D300N variant. Clinicians who come across patients with no underlying cause of NAFLD should consider genetic testing, particularly when there is a strong family history of associated pathologies. It is critical to test the *LMNA* gene when considering FPLD. If the diagnosis of FPLD is made, it is necessary to inform the patient of the possible diseases that may progress and to continually monitor their health accordingly through a multidisciplinary approach.

DISCLOSURES

Author contributions: L. Mahdi wrote the manuscript. A. Kahn edited the manuscript and revised the manuscript for intellectual content. R. Dhamija and HE Vargas revised the manuscript for intellectual content. HE Vargas is the article guarantor.

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