



Cryptogenic Cirrhosis and Sitosterolemia: A Treatable Disease If Identified but Fatal If Missed

Fateh Bazerbachi,^{*,*} Erin E. Conboy,^{†,♦}
Taofic Mounajjed,[‡] Kymberly D. Watt,^{*} Dusica Babovic-Vuksanovic,[†] Shailendra B. Patel,[§] Patrick S. Kamath^{*}

^{*} Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN. [†] Department of Clinical Genomics, Mayo Clinic, Rochester, MN.

[‡] Department of Pathology, Mayo Clinic, Rochester, MN. [§] Division of Endocrinology, Diabetes, and Metabolism, University of Cincinnati, OH.

♦ These authors contributed equally to this work.

ABSTRACT

Sitosterolemia is an autosomal recessive metabolic disease caused by mutations in *ABCG5* or *ABCG8* genes which encode for the (ATP)-binding cassette (ABC) transporters that are responsible for the trafficking of xenosterols. Liver involvement is not a recognized manifestation of this disease, and cirrhosis has been reported only once in the medical literature. We describe a fatal case of a 21-year old South Asian male who presented with decompensated cirrhosis, and biochemical abnormalities consistent with sitosterolemia. Genetic testing showed a homozygous pathogenic mutation in *ABCG5*, confirming the diagnosis. Sitosterolemia is a rare, but likely under-recognized condition, and a high degree of suspicion is imperative to make the diagnosis. We propose that sitosterolemia should be included in the differential diagnosis for patients with cryptogenic cirrhosis, especially as there are effective oral therapies to treat this condition. Newly diagnosed sitosterolemia patients should undergo a thorough hepatology evaluation and follow-up to evaluate for the presence, development, and progression of any hepatic involvement.

Key words. Cryptogenic cirrhosis. Ascites. Idiopathic cirrhosis. Sitosterolemia, Phytosterolemia. Plant sterols. Premature coronary artery disease. Macrothrombocytopenia. *ABCG5*. *ABCG8*.

INTRODUCTION

Sitosterolemia is a rarely reported disorder of lipid metabolism, first described in 1974,¹ in which plant sterols accumulate in blood and tissues due to a defect in their intestinal and hepatic excretion, resulting in variable clinical manifestations.² Physiologically, small amounts of ingested phytosterols are absorbed and circulated in the plasma,³ but are rapidly cleared by the liver. Plant sterols comprise the major dietary xenosterols humans are exposed to. In this autosomal recessive disease, these absorbed xenosterols are not cleared, but accumulate leading to tissue damage. Patel, *et al.*⁴ mapped the disease locus, *STSL*, to chromosome 2p21. Two genes, *ABCG5* and *ABCG8*, comprise the *STSL* locus, encoding adenosine triphosphate (ATP)-binding cassette (ABC) transporters sterolin-1 and sterolin-2, respectively, and biallelic pathogenic variations in *ABCG5* or *ABCG8* lead to increased intestinal absorption of phytosterols.⁵⁻⁷

Interestingly, it is estimated that less than 100 individuals with sitosterolemia have been described to date, and only one case of cirrhosis reported since the discovery of this disease.⁸ We describe the case of a 21-year old male who presented with decompensated cirrhosis, and profound hemolytic anemia. Given that he had some classic associations of sitosterolemia, including hemolytic anemia, xanthomas, and ischemic heart disease, we examined his plasma sterol profile, and the biochemical diagnosis of sitosterolemia was made.⁸ Gene sequencing of *ABCG5* and *ABCG8* confirmed the diagnosis, revealing a homozygous pathogenic variation in *ABCG5*.

CASE DESCRIPTION

A 21-year old male of Pakistani decent presented to an outside hospital with jaundice, chest pain, dyspnea on exertion, as well as worsening ascites and was referred for management of cirrhosis and liver transplantation evalua-

tion. His Model for End-Stage Liver Disease (MELD) score was 32, and was given a presumptive diagnosis of end-stage autoimmune hepatitis. A coronary CT angiography showed diffuse severe coronary disease without significant calcium deposition, leading the providers to a diagnosis of vasculitis. He was therefore treated with high dose corticosteroids for 8 weeks, without improvement on repeat coronary evaluation. Liver transplant was denied considering the lack of a unifying diagnosis for his combined ischemic heart disease and liver failure.

He was referred to our institution for a second opinion. His main symptoms were fatigue, unstable angina, and exertional dyspnea. Past history revealed that he experienced waxing and waning episodes of conjunctival icterus and change in urine color in childhood and adolescence. He was reportedly anemic during these episodes, but no further work-up was done. His daily dietary habits included consuming several portions of nuts, chocolate, fruits and vegetables per day, and he never consumed alcohol. His family history included premature death of a maternal uncle, thought to be related to a myocardial infarction at the age of 27 years, but was otherwise noncontributory (Figure 1).

Physical exam revealed a thin male in no distress. Scleral icterus, diffuse jaundice, and several spider angiomas were noted. There was no jugular venous distention or gal-

lop upon cardiac auscultation, and lungs were clear of crackles. Abdominal exam revealed large volume ascites. Musculoskeletal exam was notable for tendon xanthomas and bilateral Achilles tendon thickening. Neurologic exam demonstrated neither asterix nor other focal deficit. Eye exam revealed no Kayser-Fleischer rings.

Serologic work-up ruled out chronic causes of liver disease, including negative hepatitis B and C serology, normal iron and copper studies, and negative auto-antibodies. On admission to our hospital, the patient's hemoglobin was 8.7 g/dL, with profound reticulocytosis (578 K/mm³; 21% of red blood cells). Haptoglobin was undetectable (although its interpretation was confounded by liver disease), and lactate dehydrogenase level was 540 U/L (normal < 222 U/L) without evidence of disseminated intravascular coagulation on peripheral smear (only showed rare large platelets and thrombocytopenia). Polyspecific direct antiglobulin test and the Donath-Landsteiner test were negative, and flow cytometry ruled out paroxysmal nocturnal hemoglobinuria. Since the patient's blood pressure and serum electrolytes were normal, adrenal insufficiency was not evaluated. The patient's extensive laboratory work-up, as well as liver enzymes trend until admission to the Mayo Clinic, are noted in table 1 and figure 2. Histologic examination of a transjugular liver bi-

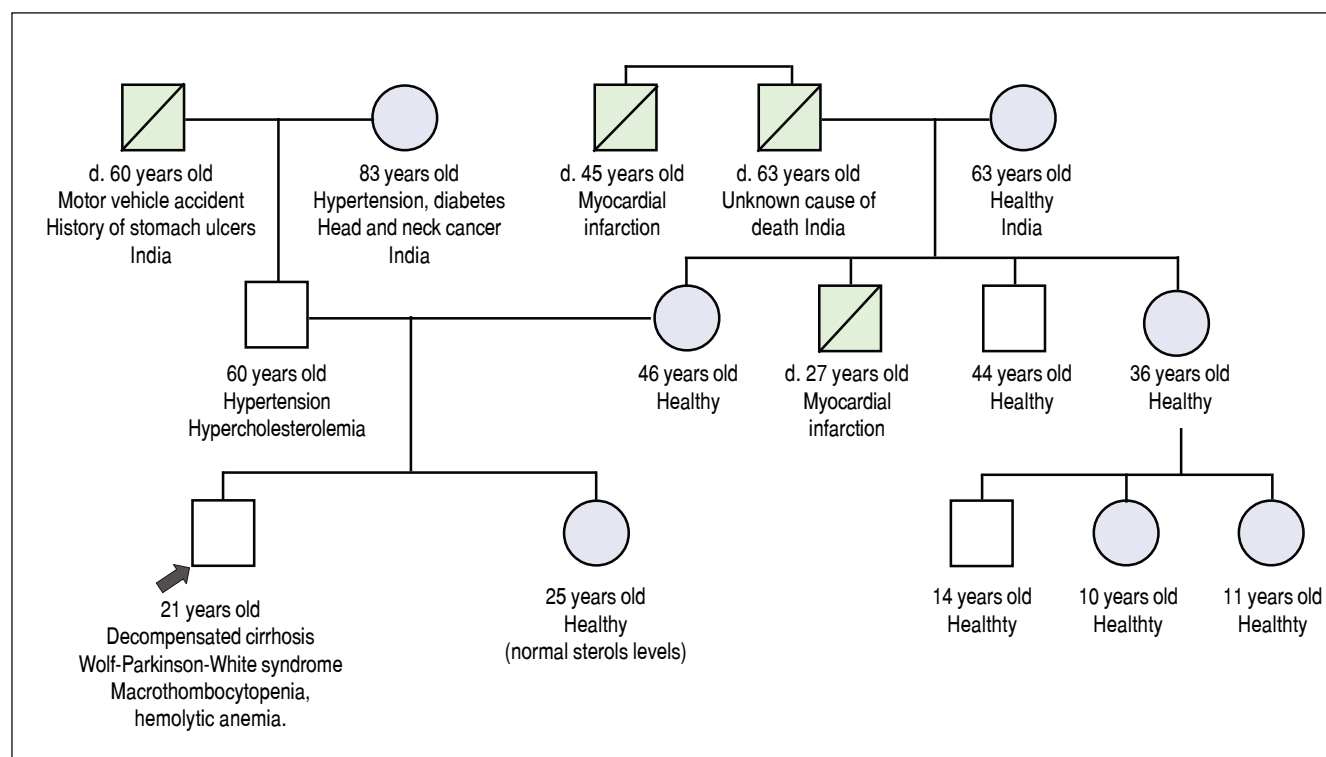
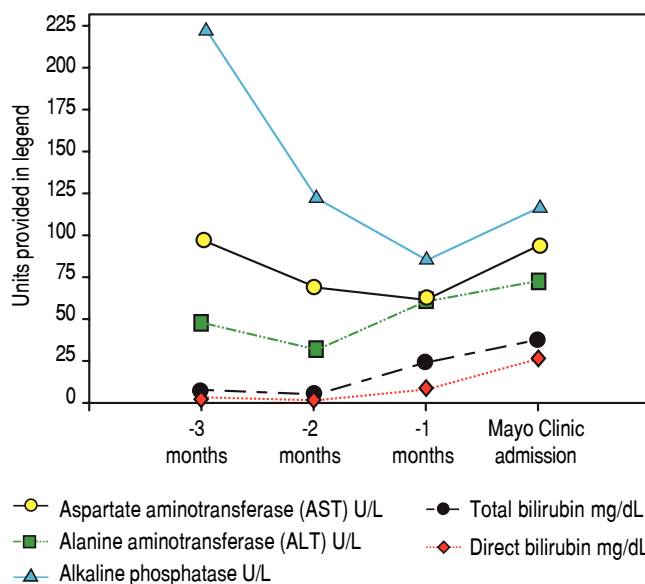


Figure 1. Family history pedigree. Black arrow indicates the patient, age 21 years at diagnosis. Mother and father are apparently healthy. Maternal uncle died at 27 years of a presumed myocardial infarction. Maternal grand-uncle died of a presumed myocardial infarction at the age of 47 years.

Table 1. Laboratory work-up on admission to Mayo Clinic.

Hemoglobin 8.9 mg/dL. MCV 106.1 fL. Platelets 55 10 ⁹ /L.
Iron 121 mcg/dL. Ferritin 232 mcg/L. Iron saturation 64%.
Sodium 128 mmol/L. Creatinine 0.6 mg/dL. Thyroid stimulating hormone (TSH) 0.9 mIU/L.
Alkaline phosphatase 117 U/L. AST 94 U/L, ALT 73 U/L. Total bilirubin 38 mg/dL (direct bilirubin 26.4 mg/dL). Gamma-glutamyl transferase 18 U/L.
INR 2.7
MELD-Na Score= 34 points.
Urine excretion of Erythritol 54 mmol/mol Cr. Urine excretion of Arabinitol 26 mmol/mol Cr. Urine excretion of Ribitol 8 mmol/mol Cr. Urine excretion of Sedoheptulose 10 mmol/mol Cr. Homocysteine level 13 mcmmol/L (normal).
Immunoglobulin G 3051 mg/dL. Anti-Smooth Muscle Antibody, Antimitochondrial Antibody, Liver/kidney microsomal antibodies, Antinuclear Antibodies, c-ANCA, p- ANCA, Antiphospholipids (IgM and IgG), Myeloperoxidase antibodies, proteinase (PR3) all negative. Alpha-1 antitrypsin level 121 mg/dL with MM phenotype. Ceruloplasmin 19.2 mg/dL with normal 24 hour urine copper.
Evaluation for Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Human Immunodeficiency Virus (HIV), Herpes simplex viruses (type 1 and 2), Parvovirus, Hepatitis B virus (HBV), Hepatitis C virus (HCV), and Hepatitis A virus (HAV) was negative. Toxoplasma and syphilis evaluation were negative.
Acid-beta glucosidase > 38 nmol/mL/h. Sphingomyelinase 11.7 nmol/mL/h. Acid-alpha glucosidase 6.9 nmol/mL/h. Galactocerebrosidase 9.4 nmol/mL/h. Alpha galactosidase >20 nmol/mL/h. Alpha L-Iduronidase 5.9 nmol/mL/h. C20 Lysophosphatidylcholine 0.08 mcg/L. C22 lysophosphatidylcholine 0.07 mcg/L. C24 Lysophosphatidylcholine 0.06 mcg/L. C26 lysophosphatidylcholine 0.08 mcg/L.
Protein electrophoresis showed polyclonal hypergammabulinemia: Total protein 6.9 g/dL. Albumin 3.4 g/dL. Alpha-1 globulin 0.2 g/dL. Alpha-2 globulin 0.6 g/dL. Beta globulin 0.5 g/dL. Gamma globulin 2.3 g/dL.
Comprehensive urine toxicology screening was negative.
Bone marrow biopsy revealed normocellularity with erythroid hyperplasia, moderately-reduced granulopoiesis, and normal megakaryopoiesis. There were no morphologic features of a myeloid neoplasm or involvement by a lymphoproliferative disorder.

**Figure 2.** Liver enzymes trend after liver decompensation until admission in the Mayo Clinic.

opsy showed established cirrhosis (Figures 3A and 3C). The hepatic acinar parenchyma also displayed marked canalicular and hepatocellular cholestasis (Figure 3B). There were occasional foci of hepatocellular parenchymal collapse. Electron microscopy confirmed the histologic finding of cholestasis and showed some increase both in the number and size of mitochondria (Figures 4A and 4B). Some increase in hepatic stellate cells was also identified (Figure 4C). No abnormal storage material was noted in hepatocytes or Kupffer cells.

Additional laboratory investigations revealed a normal lipid pattern, with a total cholesterol level of 152 mg/dL.

His outside coronary CT angiography showed complete occlusion of the proximal right coronary artery and segmental occlusions involving the medial segment of the left anterior descending artery. There were areas of collateralization, suggesting that his cardiac disease was chronic (Figure 5). Furthermore, atherosclerotic plaques, advanced for the patient's age, were noted in the abdominal and infra-renal aorta. We suspected that these lesions could represent accelerated atherosclerotic disease. Interestingly, no similar changes in the thoracic aorta were present, counter to what would be expected in a patient with extensive coronary atherosclerotic disease. Right heart catheterization revealed normal filling pressures, and slightly increased cardiac output.

In view of the tendon xanthomas, normal cholesterol levels, profound hemolytic anemia and diffuse coronary atherosclerosis, sitosterolemia was suspected. Plasma phytosterol levels were evaluated using gas chromatography-mass spectrometry (GC-MS)/GC-flame ionization

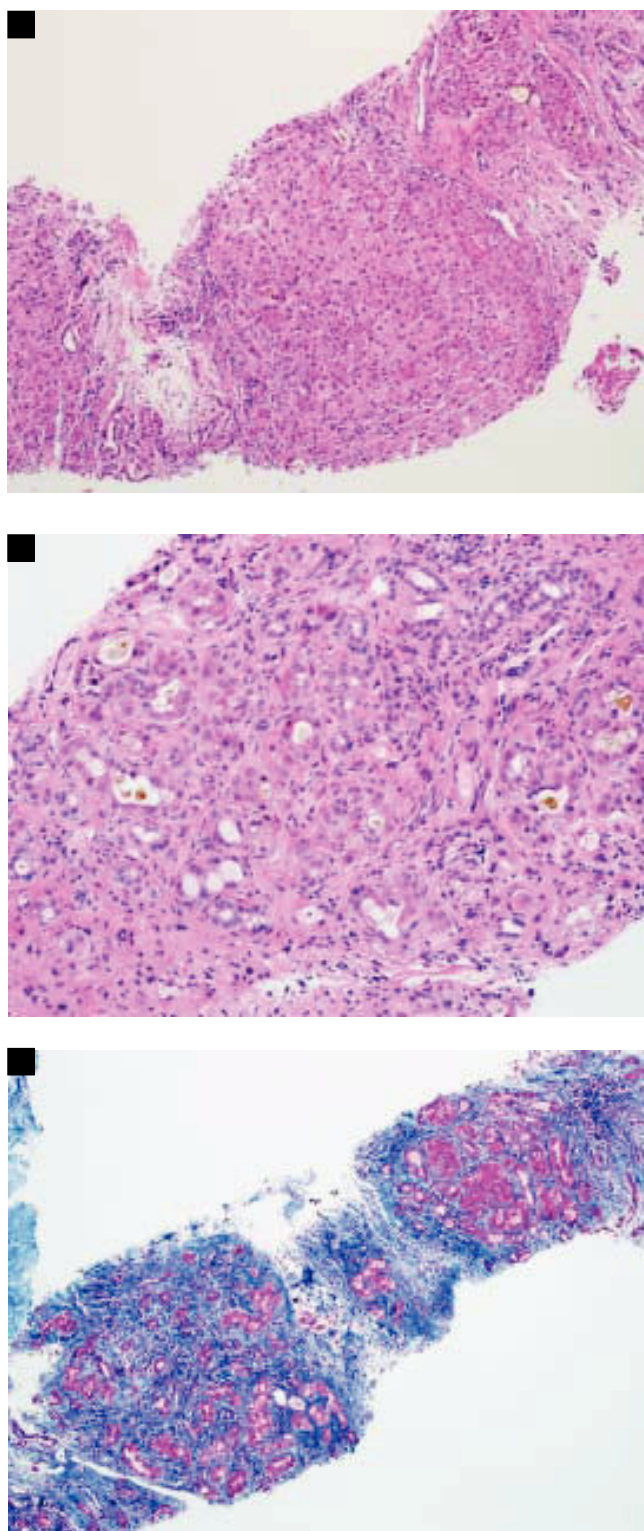


Figure 3. Liver biopsy. **A.** Low-power (100x) stained with hematoxylin and eosin (H&E) staining showing cirrhosis. **B.** High-power (200x) stained with hematoxylin and eosin (H&E) demonstrating cholestasis. **C.** Low-power (100x) Masson's Trichrome Stain showing bridging fibrosis and cirrhosis.

detection (GC-FID). Sitosterol was elevated at 17.5 mg/dL (normal < 0.5 mg/dL) as was campesterol at 7.9 mg/dL (normal < 0.7 mg/dL). Although a biochemical elevation of phytosterols is sufficient to establish the diagnosis of sitosterolemia, we opted to further confirm genetic mutations after a discussion with the patient and his family. This testing was performed on peripheral blood DNA at Fulgent Diagnostics Laboratory, and consisted of an interrogation of the *ABCG5* and *ABCG8* genes exons using next generation sequencing technology. The patient carried a homozygous pathogenic mutation in *ABCG5* at c.1336C > T, which causes a premature stop codon at amino acid position 446, leading to a predicted truncated protein. No mutations in *ABCG8* were present. Both parents, who did not undergo genetic testing, were first cousins and reportedly healthy.

Following this diagnosis, a low phytosterols diet and ezetimibe were initiated. He was approved for combined heart and liver transplant, given the ability to provide remission of sitosterolemia after transplant.⁸ Unfortunately, the patient passed away in the critical care unit due to a spontaneous intracranial bleed, while waiting for organ availability.

DISCUSSION

Our patient was initially diagnosed with autoimmune hepatitis and cirrhosis with a loss of histological hallmarks of causative disease, similar to the case reported by Miettinen, *et al.*⁸ With a high level of clinical suspicion and appropriate laboratory investigations, sitosterolemia was diagnosed. Miettinen and colleagues were the first to report cirrhosis as the primary presenting feature in a sitosterolemic patient, making our case the second in literature, and suggesting that this association is not coincidental. The known classic features of sitosterolemia are the presence of xanthomas despite normal cholesterol levels, macrothrombocytopenia, hemolytic anemia and premature atherosclerotic disease (Table 2). Prior to this report, end-stage liver disease has not been recognized as a cardinal feature of sitosterolemia, and we believe that our observation and review are pivotal in raising awareness to this lethal, and potentially reversible disease. The clinical presentations are variable and range from being asymptomatic to severe. Hemolysis is a frequent occurrence in affected individuals and is thought to be related to the effect of sitosterol on red cell membrane stability, and this feature may be episodic, interrupting periods of normality.⁹ The presence of tendon xanthomas without elevated LDL-cholesterol should raise suspicion of sitosterolemia (grade III/B recommendation).¹⁰ Adrenal insufficiency,¹¹ spinal cord compression¹² and splenomegaly^{13,14} are also reported associations.

Biliary and enterocyte sterol handling is critical for the excretion of cholesterol, as well as non-cholesterol sterols, such as phytosterols.¹⁵ To date, the ABCG5/ABCG8 transporter apparatus is the only recognized system to partici-

pate in the process of phytosterol excretion. ABCG5 and ABCG8 form heterodimer transporters that are located in the apical cell membranes of the bile ducts and intestinal enterocytes. Sitosterolemia patients have biallelic pathogen-

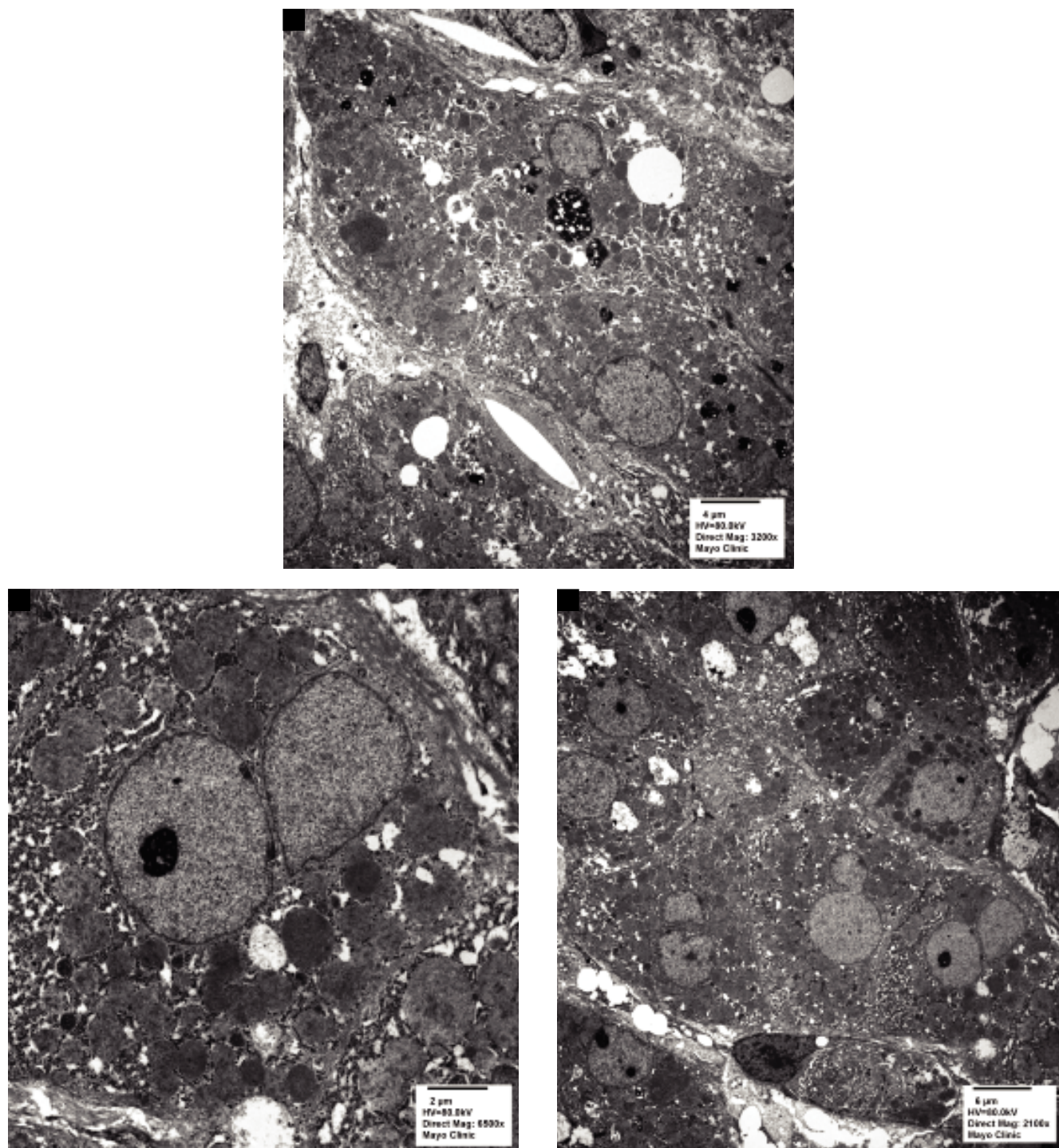


Figure 4. Electron microscopy images. **A.** Magnification (3200x): Cholestatic pigment and occasional lipid droplets. **B.** Magnification (6,500x): Increased and enlarged mitochondria. **C.** Magnification (2,100x): Prominent hepatic stellate cells.

ic mutations in the genes, *ABCG5* or *ABCG8*, causing loss of function of the *ABCG5/ABCG8* transporters,⁵⁻⁷ which causes severe elevation in plasma phytosterols,

This accumulation of phytosterols could potentially lead to liver dysfunction phenotype of sitosterolemia. An association between sitosterol levels and cholestatic liver

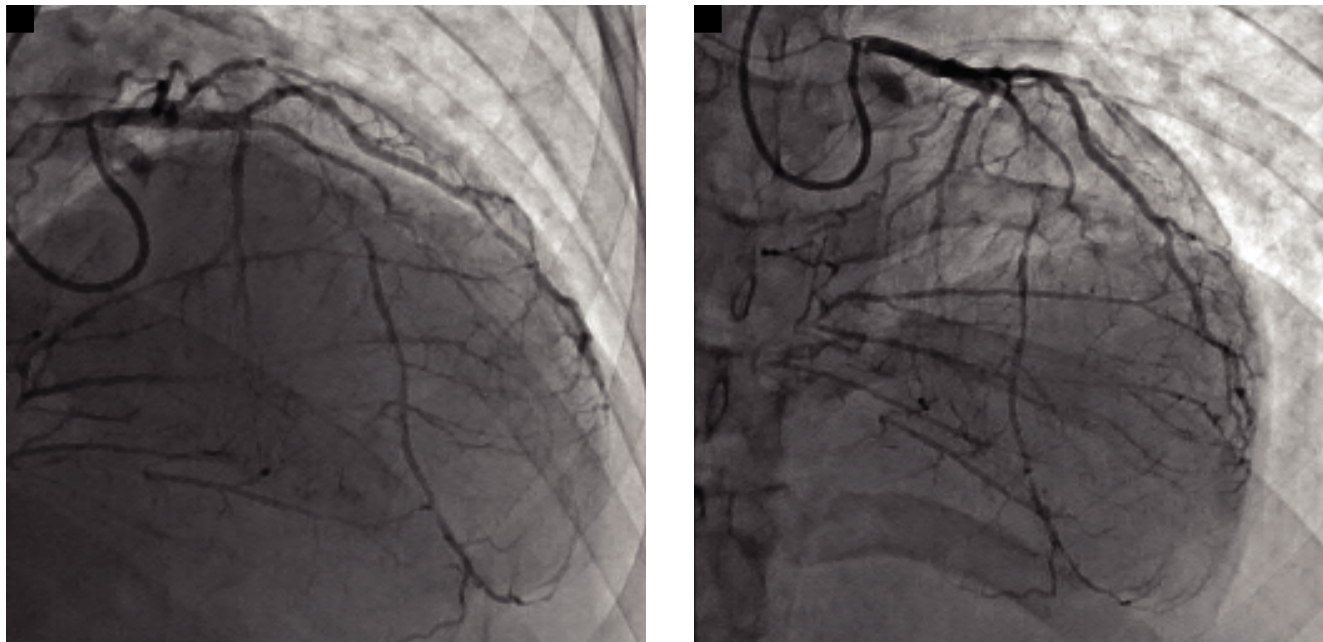


Figure 5. Coronary angiogram images. **A-B.** Right and left anterior oblique cranial views, respectively, of the diffusely stenosed left anterior descending coronary artery, as compared with a relatively normal diagonal branch, and demonstrating significant collaterals that suggests an atretic right coronary artery.

Table 2. The range of clinical features currently seen in sitosterolemia compared to the clinical features of our patient.

Clinical feature	Relative frequency in literature	Presence in our case
Arthralgia	~30%	Yes
Tendon xanthomas	~30%	Yes (bilateral thickening of Achilles tendons on ultrasound)
Elevated total cholesterol (mild)	~30%	No
Anemia (mild)	~30%	Yes (Severe)
Thrombocytopenia	~30%	Yes
Elevated liver enzymes (<3 upper limit of normal)	~30%	Yes
Thickened cardiac valves	< 10%	No
Carotid bruit	< 10%	No (No stenosis on carotid ultrasound)
Premature coronary disease	< 10%	Yes (Severe and diffuse)
Sudden premature death	< 10%	Yes (Due to spontaneous intracerebral bleed and multiorgan failure, not myocardial infarction)
Liver cirrhosis	< 1%	Yes (second known reported case)
Diarrhea (ulcerative colitis)	< 1%	Unknown but possible (patient had an episode of bloody diarrhea prior to admission)
Vitamin D deficiency in childhood	Not reported	Yes
Wolff-Parkinson-White	Not reported	Yes
Nephrolithiasis	Not reported	Yes

Modified from Patel, et al.²

disease has been found in neonates who were administered sitosterol-containing lipid emulsions for TPN with increased incidence in a dose-dependent fashion. Kurvinen, *et al.* concluded that elevated phytosterols, especially stigmasterol, may be an independent risk factor for liver disease in these patients.¹⁶ Similarly, in a more recent study by Hukkinen, *et al.*, the authors found that among children with intestinal failure, parenteral plant sterols accumulate in the liver and relate to hepatic injury, portal inflammation, and liver fibrosis. The authors proposed a role for sterols in promoting liver damage.¹⁷

The underlying genetic alterations leading to sitosterolemia are important to consider, as it delineates the fundamental underlying cause of the disease. Our patient had a homozygous variant in the *ABCG5* gene (NM_022436.2) c.1336C > T. At the protein level, the nonsense variation p.Arg446* encodes for a premature stop codon at position 446, leading to protein truncation. In the other reported case of sitosterolemia-associated cirrhosis, the patient had a mutation in *ABCG8*, making this the first case of sitosterolemia-associated cirrhosis in a patient with *ABCG5* gene. To support the pathogenicity of this variation, there are two other patients with the same homozygous alteration diagnosed with sitosterolemia,^{18,19} although liver disease was not described. In the Exome Aggregation Consortium (ExAC) database, this variation is reported in 8 of 15,882 healthy individuals with an allele frequency of 0.0005%, further supporting evidence that this pathogenic mutation has a frequency in the general population consistent with a recessive condition (accessed on 10/6/2016).²⁰

Sitosterolemia is thought to be a rare disease, however the true prevalence is unknown; the current estimation is 1 in 1,000,000.²¹ A Chinese group reported 13 patients from 8 separate families over a seven year period who presented with sitosterolemia to a single institution.²² Therefore, it seems that sitosterolemia may not be as rare as originally thought, and we believe that screening is warranted in patients presenting with cryptogenic cirrhosis with any cardinal manifestation, and may even be important before symptoms manifest altogether, considering the simple effective interventions (e.g. diet modifications, ezetimibe treatment) that may alter a sinister end-stage outcome. Although the relationship between sitosterolemia and liver disease has not been previously firmly established, this feature of clinical variability, termed variable expressivity, is common in many genetic disorders, including inborn errors of metabolism.²³ In addition, this tenet of variable expressivity could account for the variability of clinical features in this disease. Our case suggests that the progressive liver dysfunction phenotype association is real and requires further study. A high index of suspicion is needed to make the diagnosis, as standard lipid

testing does not identify this disorder, and phytosterols specific evaluation must be performed [Gas chromatography (GC) or high-performance liquid chromatography (HPLC)] separation of sterols. Alternatively, patients who are diagnosed with sitosterolemia should undergo a hepatology evaluation to determine the extent of liver involvement, and interval liver follow-up should be pursued. This is mainly directed at evaluating the presence of increased liver enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma glutamyl transferase), the integrity of the hepatic functions (e.g. prothrombin time, bilirubin, and albumin), as well as liver stiffness measurement as a surrogate for liver fibrosis (e.g. transient elastography). This will allow for the evaluation of the presence, development, and progression of hepatic affliction, which may modify the aggressiveness of sitosterolemia therapy. Furthermore, this will facilitate the recognition of end stage liver disease, and appropriate referral to a liver transplant center prior to decompensation, if needed.

This case presents novel and important observations regarding this possibly under-recognized disease; idiopathic/cryptogenic cirrhosis is not an uncommon diagnosis for some end-stage liver disease subjects. The association of cirrhosis and *ABCG5* mutation has not been previously described. Miettinen, *et al.* hypothesized that a mutation in either *ABCG5* or *ABCG8* may cause misfolded proteins in the liver to accumulate and induce injury. However, their immunohistochemistry data did not support that hypothesis. The mutation detected in our patient, c.1336C > T is theorized to result in nonsense mediated RNA decay, meaning that the RNA would be targeted for degradation before translation occurs.²⁴ As a result, we would hypothesize that staining for *ABCG5* in liver tissue would be completely absent. Unfortunately, there was no tissue available to test for this possibility. In the only other reported case, liver transplantation resulted in significant amelioration in plant sterol values.⁸ Miettinen and colleagues hypothesized that transplantation of a nonsitosterolemic liver seems to prevent the accumulation of phytosterols, despite a persistent intestinal defect.⁸ The restoration of hepatobiliary excretion mechanisms remains a major pathway for sterol excretion and are sufficient to alleviate the phytosterolemia. In a mouse model of sitosterolemia, an intestinal-only restoration also seems to reduce the xenosterol burden, suggesting any one pathway is sufficient to make an impact on the biochemistry.²⁵

In summary, we report a novel case of sitosterolemia and cirrhosis, confirmed by biallelic mutations in *ABCG5*. We postulate that liver damage is likely secondary to the harmful effects of high plant sterols levels, with potential contribution from misfolded mutant protein accumulation in the hepatic cells. Increased aware-

ness of the disorder is needed to identify new affected patients and establish more accurate frequency estimation of sitosterolemia. Consideration for phytosterol testing for patients presenting with cryptogenic cirrhosis, particularly if they display other cardinal features of sitosterolemia should take place. A thorough hepatology evaluation for those who are newly diagnosed with sitosterolemia should also be performed, to monitor for the occurrence, as well as progression of liver disease. The magnitude of noble organ damage should guide the escalation of therapy, starting from dietary modification and ezetimibe use,^{2,26} to surgical ileal bypass, and perhaps liver transplantation, if ongoing hepatic damage is not subdued with noninvasive approaches.

ACKNOWLEDGEMENTS

We are grateful to Dr. Lisa Schimmenti and Dr. Robert Steiner for their helpful and informative discussions regarding this case, to Dr. Ian Cheng-Yi Chang for reviewing our coronary angiography images, and to Dr. Samir Haffar for his review of the manuscript.

FINANCIAL SUPPORT AND CONFLICT OF INTEREST DISCLOSURE

No financial support or conflict of interest for any of the authors is present.

REFERENCES

- Bhattacharyya AK, Connor WE. Beta-sitosterolemia and xanthomatosis. A newly described lipid storage disease in two sisters. *J Clin Invest* 1974; 53: 1033-43. doi: 10.1172/JCI107640.
- Patel SB, Salen G. Sitosterolemia: xenophobia for the body. In: Vissers MN, Kastelein JJP, Stroes ES (eds.). Evidence-based Management of Lipid Disorders. Harley: tfm Publishing Ltd; 2010. p. 217-30.
- Salen G, Ahrens EH Jr, Grundy SM. Metabolism of beta-sitosterol in man. *J Clin Invest* 1970; 49: 952-67. doi: 10.1172/JCI106315.
- Patel SB, Salen G, Hidaka H, Kwiterovich PO, Stalenhoef AFH, Miettinen TA, Grundy SM, et al. Mapping a gene involved in regulating dietary cholesterol absorption. The sitosterolemia locus is found at chromosome 2p21. *J Clin Invest* 1998; 102: 1041-4. doi: 10.1172/jci3963.
- Lu K, Lee MH, Hazard S, Brooks-Wilson A, Hidaka H, Kojima H, Ose L, et al. Two genes that map to the STSL locus cause sitosterolemia: genomic structure and spectrum of mutations involving sterolin-1 and sterolin-2, encoded by ABCG5 and ABCG8, respectively. *Am J Hum Genet* 2001; 69: 278-90.
- Lee MH, Lu K, Hazard S, Yu H, Shulenin S, Hidaka H, Kojima H, et al. Identification of a gene, ABCG5, important in the regulation of dietary cholesterol absorption. *Nat Genet* 2001; 27: 79-83. doi: 10.1038/83799.
- Berge KE, Tian H, Graf GA, Yu L, Grishin NV, Schultz J, Kwiterovich P, et al. Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. *Science* 2000; 290: 1771-5.
- Miettinen TA, Klett EL, Gylling H, Isoniemi H, Patel SB. Liver transplantation in a patient with sitosterolemia and cirrhosis. *Gastroenterology* 2006; 130: 542-7.
- Fazio S, Linton MF. Evidence-based Management of Lipid Disorders. 2011.
- Kurvinen A, Nissinen MJ, Andersson S, Korhonen P, Ruuska T, Taimisto M, Kalliomaki M, et al. Parenteral plant sterols and intestinal failure-associated liver disease in neonates. *J Pediatr Gastroenterol Nutr* 2012; 54: 803-11. doi: 10.1097/MPG.0b013e3182474118.
- Mushtaq T, Wales JK, Wright NP. Adrenal insufficiency in phytosterolaemia. *Eur J Endocrinol* 2007; 157(Suppl. 1): S61-5. doi: 10.1530/EJE-07-0222.
- Hatanaka I, Yasuda H, Hidaka H, Harada N, Kobayashi M, Okabe H, Matsumoto K, et al. Spinal cord compression with paraplegia in xanthomatosis due to normocholesterolemic sitosterolemia. *Ann Neurol* 1990; 28: 390-3. doi: 10.1002/ana.410280316.
- Salen G, Shefer S, Berginer V. Familial diseases with storage of sterols other than cholesterol: Cerebrotendinous xanthomatosis and sitosterolemia with xanthomatosis. In Stanbury JB, Wyngaarden JB, Frederickson DS, et al. (Eds): The Metabolic Basis of Inherited Disease. ed 5. New York: McGraw-Hill Book Co; 1982, pp. 713-24.
- Hidaka H, Nakamura T, Aoki T, Kojima H, Nakajima Y, Kosugi K, Hatanaka I, et al. Increased plasma plant sterol levels in heterozygotes with sitosterolemia and xanthomatosis. *J Lip Res* 1990; 31: 881-8.
- Gylling H, Vuorio M, Farkkila M, Miettinen TA. The metabolism of cholesterol in primary biliary cirrhosis. *J Hepatol* 1996; 24: 444-51.
- Kurvinen A, Nissinen MJ, Andersson S, Korhonen P, Ruuska T, Taimisto M, Kalliomaki M, et al. Parenteral plant sterols and intestinal failure-associated liver disease in neonates. *J Pediatr Gastroenterol Nutr* 2012; 54: 803-11. doi: http://dx.doi.org/10.1097/MPG.0b013e3182474118.
- Hukkinen M, Mutanen A, Nissinen M, Merras-Salmio L, Gylling H, Pakarinen MP. Parenteral Plant Sterols Accumulate in the Liver Reflecting Their Increased Serum Levels and Portal Inflammation in Children With Intestinal Failure. *J Parenter Enteral Nutr* 2016;9:9. doi: http://dx.doi.org/10.1177/0148607116637855.
- Li Y, Salfelder A, Schwab KO, Grünert SC, Velten T, Lütjohann D, Villavicencio-Lorini P, et al. Against all odds: blended phenotypes of three single-gene defects. *Eur J Hum Genet* 2016; 24: 1274-9.
- Mannucci L, Guardamagna O, Bertucci P, Pisciotto L, Libertosoli L, Bertolini S, Irace C, et al. Beta-sitosterolaemia: a new nonsense mutation in the ABCG5 gene. *Eur J Clin Invest* 2007; 37: 997-1000.
- Lek M, Karczewski K, Minikel E, Samocha K, Banks E, Fennell T, O'Donnell-Luria A, et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature* 2016; 536: 285-91. doi:10.1038/nature19
- Garg A. Dyslipidemias: Pathophysiology, Evaluation and Management. Springer; 2015.
- Wang Z, Cao L, Su Y, Wang G, Wang R, Yu Z, Bai X, et al. Specific macrothrombocytopenia/hemolytic anemia associated with sitosterolemia. *Am J Hematol* 2014; 89: 320-4. doi: http://dx.doi.org/10.1002/ajh.23619.
- Nussbaum RL, McInnes RR, Willard HF. Thompson & Thompson genetics in medicine. Elsevier Health Sciences; 2015.

24. BIOBASE biological databases. Available at: URL. Access: 2016/10/09.
25. Solca C, Tint GS, Patel SB. Dietary xenosterols lead to infertility and loss of abdominal adipose tissue in sterolin-deficient mice. *J Lipid Res* 2013; 54: 397-409. doi: 10.1194/jlr.M031476.
26. Musliner T, Cselovszky D, Sirah W, McCrary Sisk C, Sapre A, Salen G, Lutjohann D, et al. Efficacy and safety of ezetimibe 40 mg vs. ezetimibe 10 mg in the treatment of patients with homozygous sitosterolaemia. *Int J Clin Pract* 2008; 62: 995-1000. doi: <http://dx.doi.org/10.1111/j.1742-1241.2008.01786.x>.

Correspondence and reprint request:

Fateh Bazerbachi, M.D.
Division of Gastroenterology and Hepatology,
Mayo Clinic, College of Medicine,
200 First Street SW, Rochester, Minnesota 55905.
Ph.: (507) 284-1825. Fax: (507) 284-0538.
E-mail: Bazerbachi.fateh@mayo.edu