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Case Studies

# Severe hypercholesterolemia and phytosterolemia with extensive xanthomas in primary biliary cirrhosis: Role of biliary excretion on sterol homeostasis

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**Abstract:** Primary biliary cirrhosis (PBC) is an autoimmune, chronic, cholestatic liver disease that affects primarily women. PBC is commonly associated with hypercholesterolemia that has been associated with cholestasis. We report an exceptionally high blood cholesterol and phytosterols with just mild cholestasis indicating a selective defect in sterol biliary secretion in a patient with PBC.


## Background

Primary biliary cirrhosis (PBC) is an autoimmune, chronic, cholestatic liver disease that primarily affects women. Histopathologically, PBC is characterized by portal inflammation and immune-mediated destruction of the intrahepatic bile ducts. Serologically, PBC is characterized by the presence of antimitochondrial antibodies, which are present in 90 to 95% of patients and are often detectable years before clinical signs appear.[1] Pruritus can be the most distressing symptom.[2] Other common findings in PBC include fatigue, hypothyroidism, osteopenia, and coexisting autoimmune diseases, including Sjogren's syndrome and scleroderma.[3] PBC is commonly associated with hypercholesterolemia and marked alterations of the enterohepatic circulation of bile acids.[4] Cholesterol precursors are lower in PBC patients than in control subjects, probably reflecting decreased cholesterol synthesis, whereas increased level of phytosterols or plant sterols (eg, campesterol and sitosterol) and cholestanol, a biliary cholesterol metabolite, are mainly from impaired biliary elimination.[5] Plant sterols and cholestanol plasma concentrations in humans are only about 0.5% of the respective cholesterol values in normal subjects, and this is believed to be produced by a differential intestinal absorption among sterols. Intestinal sterol absorption is mediated by several transporter proteins located at the intestinal brush border membrane. All intestinal sterols are taken up by the enterocyte to a similar extent through the Niemann-Pick C1 Like 1 transporter,[6] and the ATP-binding cassette (ABC) transporters G5 and G8 actively efflux plant sterols back into the intestinal lumen. However, cholesterol is mainly incorporated to chylomicrons and poorly eliminated by ABCG5/G8 transporters.[7] In addition, ABCG5/G8s are located at the canalicular membranes of hepatocytes, where they facilitate efflux of cholesterol and plant sterols into bile.[8]

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## Case report

A 43-year-old woman was referred to our lipid clinic for hypercholesterolemia and pruritus. The patient reported jaundice, fatigue, and generalized pruritus in the past 6 months. Pruritus was especially significant in both hands during the past month. She had no personal or family history of hyperlipidemia or premature cardiovascular disease. Two years ago, total cholesterol concentration was in the normal range (194 mg/dL). A study by the Liver Unit of our institution revealed conjugated bilirubin 1.56 mg/dL, alkaline phosphatase 714 U/L, and total cholesterol 1369 mg/dL. The diagnosis of PBC was confirmed with the presence of antimitochondrial antibodies, and compatible histological liver findings. The liver biopsy showed enlarged portal triads that were infiltrated with mixed chronic inflammatory cells including lymphocytes, eosinophils, and neutrophils, and with inflammation extending to the hepatic parenchyma. Some portal triads showed destruction of the bile ducts without substantial periportal fibrosis. Stage II primary biliary cirrhosis was the pathological diagnosis. The patient underwent treatment with cholestyramine 8 g/day and ursodeoxycholic acid 1500 mg/day without any clinical or biochemical improvement after 3 months, when she was referred to our clinic for lipid management. Physical examination revealed jaundice, interdigital xanthomas (Fig. 1A), xanthelasmas (Fig. 1B), and palmar xanthomas (Fig. 1C and 1D). Sonography of the Achilles tendons did not show enlargement or lipid accumulation compatible with tendon xanthomas. Her total cholesterol was 1404 mg/dL, triglycerides 146 mg/dL, high-density lipoprotein cholesterol 58 mg/dL, apolipoprotein B 189 mg/dL, conjugated bilirubin 2.3 mg/dL, and alkaline phosphatase 1362 U/L. *APOE* genotype was E3/E3. Platelet count and mean platelet volume were normal ($379 \times 10^3/\mu L$ and 9.2 fL, respectively). Two months after initiating treatment with rosuvastatin 20 mg/day, fenofibrate 145 mg/day, and ezetimibe 10 mg/day, the patient's total cholesterol level was 516 mg/dL, triglycerides 159 mg/dL, high-density lipoprotein cholesterol 96 mg/dL, conjugated bilirubin 2.07 mg/dL, and alkaline phosphatase 1089 U/L. Lipoproteins isolation before and after lipid-lowering treatment was assessed by fast protein liquid chromatography (FPLC; AKTA Purifier UPC 10 FPLC system, GE Healthcare) and showed the presence of a large amount of lipoprotein X, characterized by its high content of phospholipids (66% by weight) and cholesterol (25%) (Fig. 2). Serum levels of noncholesterol sterols (phytosterol, cholesterol precursors, and bile acids precursors) were also measured by high-performance liquid chromatography mass spectometry[9] before and after lipid-lowering treatment in the patient and in 10 normolipemic age-matched women (Table 1). All sterols were highly elevated in the patient in comparison with normolipemic controls. This increase was especially relevant for cholestanol and plant sterols that were 10 to 30 times higher in the patient than in controls, even after ezetimibe treatment. These differences remained highly significant even after adjusting for total cholesterol. Cholesterol precursors (desmosterol and lanosterol) were in the normal range after adjustment for total cholesterol and decreased, as expected, with statin treatment. Desmosterol/cholestanol and desmosterol/sitosterol ratios, good surrogates of hepatic synthesis/intestinal absorption balance,[10] were highly decreased in the patient (Table 1). DNA was extracted with standard procedures from ethylenediaminetetraacetic acid blood samples. Promoters, coding regions, and intron-exon of *ABCG5*

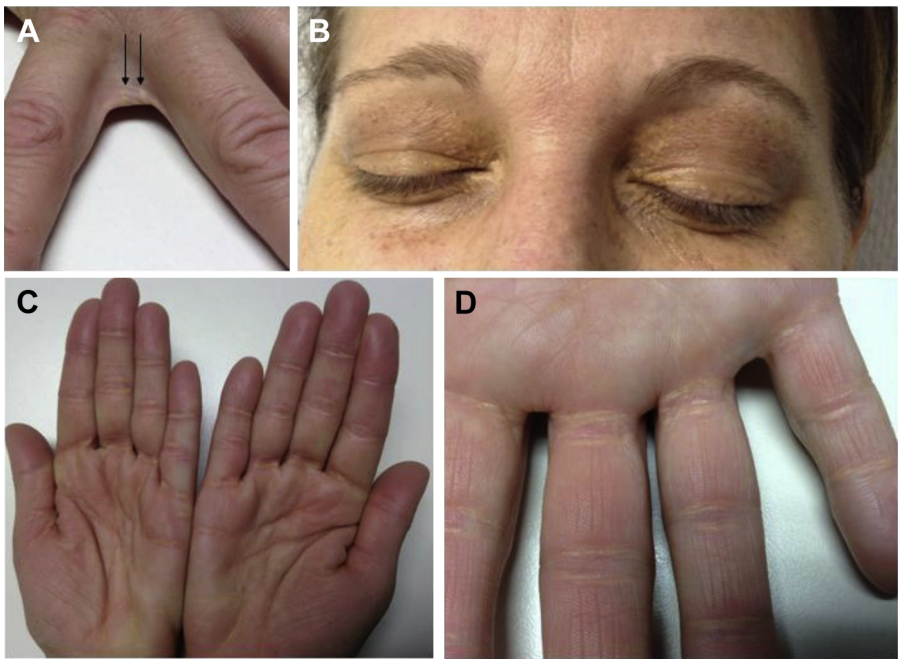


**Figure 1** (A) Interdigital xanthomas. (B) Xanthelasmas. (C, D) Palmar xanthomas.