Clinical, Cosmetic and Investigational Dermatology

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CASE REPORT

From Xanthomas to Genetic Diagnosis: A Case Report of Sitosterolemia in an Infant with a Homozygous ABCG5 c.1166G>A (p.Arg389His) Variant

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Introduction: Sitosterolemia is a rare autosomal recessive disorder characterized by disrupted lipid metabolism and elevated plasma plant sterol levels. Clinical manifestations often include cutaneous and tendon xanthomas and hypercholesterolemia; delayed diagnosis can lead to cardiovascular disease and hematological abnormalities. This case report describes an 11-month-old female infant with sitosterolemia who presented with xanthomas appearing around 6 months of age. Genetic sequencing identified a homozygous *ABCG5* c.1166G>A (p.Arg389His) mutation. This report aims to discuss the clinical features and genetic diagnosis of sitosterolemia caused by *ABCG5* mutations, highlighting the challenges and key characteristics for early diagnosis to improve clinical awareness.

Case and Methods: Clinical data of a pediatric patient with sitosterolemia caused by a homozygous *ABCG5* gene mutation were retrospectively analyzed.

Results: An 11-month-old female infant developed linear xanthomas in the skin folds of her ankles at approximately 6 months of age, which progressively worsened. Blood tests revealed significantly elevated total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels. Sequencing of coding regions for genes associated with familial hypercholesterolemia and sitosterolemia identified a homozygous *ABCG5* mutation: c.1166G>A (p.Arg389His). Sanger sequencing confirmed that this variant was inherited from each parent in a heterozygous state. The diagnosis of sitosterolemia was confirmed based on genetic testing (*ABCG5/ABCG8*), lipid profile results, and clinical presentation.

Conclusion: Sitosterolemia should be suspected in patients presenting with cutaneous xanthomas, prompting thorough investigation including lipid profiling, genetic testing, and plasma plant sterol quantification to avoid misdiagnosis as familial hypercholesterolemia (FH).

Keywords: sitosterolemia, homozygous, *ABCG5*Gene, xanthomas, hypercholesterolemia, low-density lipoprotein cholesterol

Introduction

Sitosterolemia is a rare inherited lipid metabolism disorder caused by biallelic (homozygous or compound heterozygous) pathogenic mutations in either the *ABCG5* or *ABCG8* gene. This leads to increased intestinal absorption of plant sterols and impaired biliary sterol excretion.[1,2] *ABCG5* mutations are more common in Asian patients, whereas *ABCG8* mutations predominate in Caucasian populations.[3] Children often initially present with xanthomas, which leads to a high rate of misdiagnosis as familial hypercholesterolemia (FH).

Case Report

An 11-month-old female infant was referred to our dermatology clinic for progressively enlarging xanthomas on both ankles over a 5-month period. The parents first noticed faint yellow papulonodular lesions on the infant's ankles at 6

Received: 5 August 2025
Accepted: 21 November 2025
Published: 28 November 2025

months of age, which gradually increased in size and coalesced into linear configurations. There was no history of fever, arthralgia, anemia, or bleeding tendencies. Family history was unremarkable: both parents were healthy with normal lipid profiles, denied consanguinity, and reported no family history of hyperlipidemia.

Physical examination revealed normal growth and development (weight: 9.1 kg, height: 72 cm). Firm, linear xanthomas (approximately 0.5–1.0 cm in size) were observed on both ankles (Figure 1A). Cardiopulmonary and abdominal examinations were normal, with no hepatosplenomegaly. Laboratory investigations showed: Total Cholesterol 8.22 mmol/L (↑, reference range 0–5.18 mmol/L); LDL-C 6.81 mmol/L (↑, reference range 0–3.37 mmol/L); Apolipoprotein B 1.73 g/L (↑, reference range 0.60–1.14 g/L). Complete Blood Count: Red Blood Cell count 5.52 $\times 10^{12}$/L (↑, reference range 4.0–5.5$\times 10^{12}$/L); Hematocrit 0.434 (↑, reference range 0.3–0.41); Red Cell Distribution Width 15.40% (↑, reference range 0–15%). Renal Function: Bicarbonate 17.7 mmol/L (↓, reference range 22.0–29.0 mmol/L). C-reactive Protein <2.00 mg/L (reference <8.00 mg/L); Complement C3 1.09 g/L (reference 0.70–1.40 g/L); Complement C4 0.240 g/L (reference 0.100–0.40 g/L); Alanine Aminotransferase 33.3 U/L (reference 8.0–71.0 U/L); Aspartate Aminotransferase 63.1 U/L (reference 21.0–80.0 U/L); Total Protein 69.5 g/L (reference 55.0–75.0 g/L); Albumin 44.1 g/L (reference 39.0–54.0 g/L); Globulin 25.4 g/L (reference 10.0–30.0 g/L). Plant sterol concentration testing was unavailable locally; therefore, plasma plant sterol levels could not be determined.

Genetic testing was performed on peripheral blood samples from the patient and her parents. Sequencing of coding regions for genes associated with FH and sitosterolemia was conducted on the Illumina platform. Data analysis and validation of suspected pathogenic mutations were performed by KingMed Diagnostics. The average sequencing depth for the targeted exons and their flanking 5bp regions was ≥200X, with ~99.5% of bases covered at >20X. Analysis against the gnomAD database indicated that the identified c.1166G>A (p.Arg389His) variant is a missense mutation in the *ABCG5* coding region, revealing a homozygous *ABCG5* mutation: c.1166G>A (p.Arg389His). Sanger sequencing confirmed that both parents were heterozygous carriers (Figure 1B), consistent with autosomal recessive inheritance, and neither parent exhibited clinical symptoms.

Diagnosis

Sitosterolemia (based on typical xanthomas, hypercholesterolemia, and homozygous *ABCG5* gene mutation).

Treatment and Outcome

The patient tragically died due to accidental drowning before treatment could be initiated. No autopsy was performed.

Discussion

The global incidence of sitosterolemia is estimated to be between 1/500,000 and 1/1,000,000, with approximately 200 cases reported worldwide to date.[4] The condition was first described in 1974 by Bhattacharyya and Conner in two sisters with tendon and tuberous xanthomas and elevated plasma plant sterol levels.[5] Berge et al first reported the association of sitosterolemia with mutations in the *ABCG5/ABCG8* genes.[6] The *ABCG5* and *ABCG8* genes encode the sterol transporters sterolin-1 and sterolin-2, respectively. These proteins form a heterodimeric complex responsible for effluxing plant sterols from enterocytes into the intestinal lumen and from hepatocytes into the bile ducts, maintaining low levels of plant sterol absorption.[6] Mutations in *ABCG5* or *ABCG8* lead to increased intestinal absorption and reduced biliary excretion of plant sterols, resulting in their accumulation in the blood and tissues.

This case demonstrates typical features: early-onset xanthomas (6 months), hypercholesterolemia, and a homozygous *ABCG5* c.1166G>A (p.Arg389His) mutation. The *ABCG5* gene is located on chromosome 2p21, spans 26,368 base pairs, and contains 13 exons. The c.1166G>A mutation in this patient is located in exon 9, resulting in the substitution of arginine (Arg) with histidine (His) at position 389 of the protein. The gnomAD database reports no homozygous individuals for this specific variant. Among reported Asian cases of *ABCG5*-related sitosterolemia, c.1166G>A (p.Arg389His) is one of the common variants.[7–9] Sitosterolemia exhibits significant phenotypic heterogeneity, with some patients being almost entirely asymptomatic. Tendon and tuberous xanthomas are hallmark features, commonly occurring on the Achilles tendons, knees, elbows, and buttocks; infants often present with multiple xanthomas. Patients with sitosterolemia are at risk for premature atherosclerosis due to elevated plasma cholesterol and plant sterols, which can

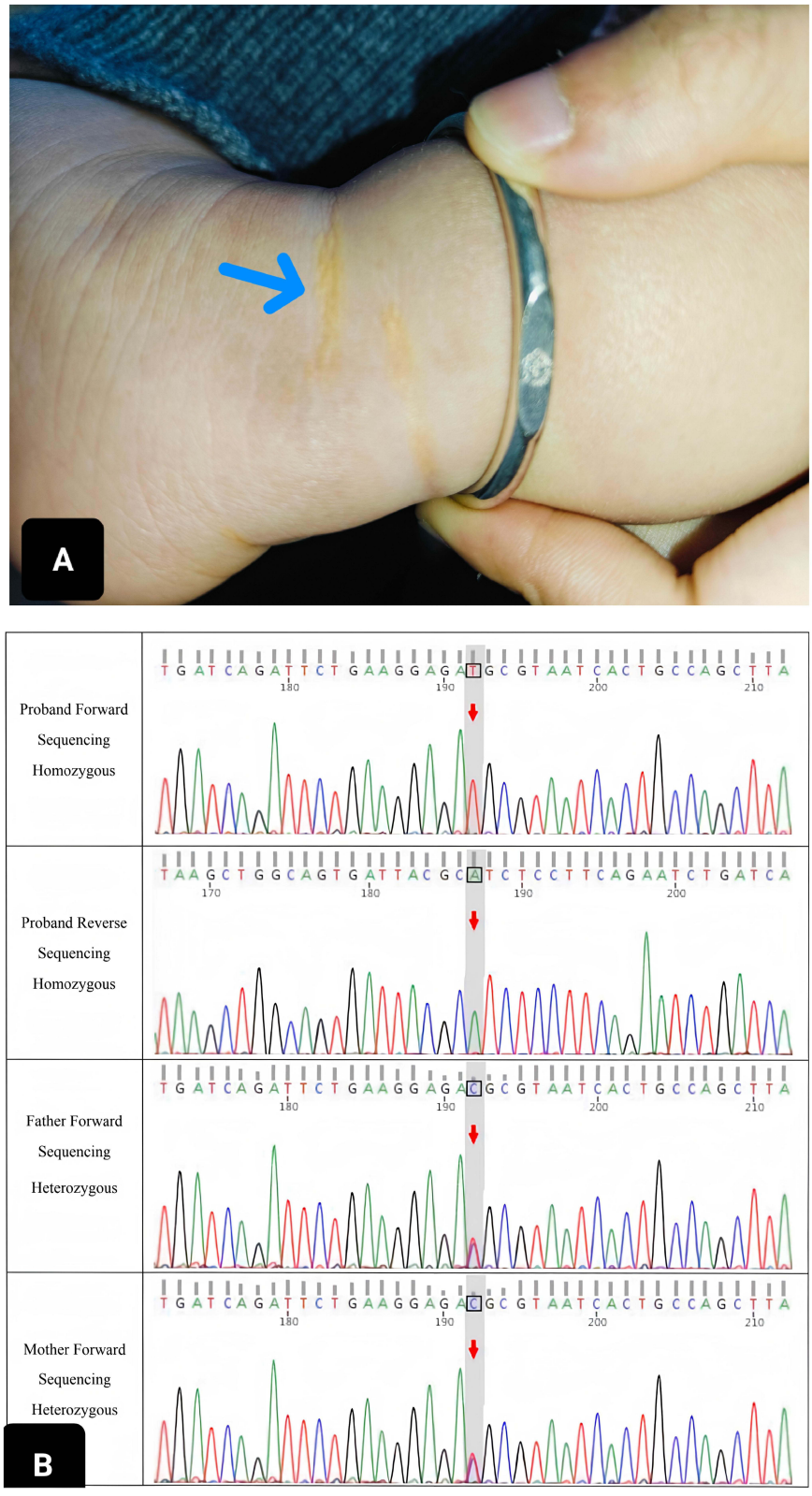

Figure 1 (**A**) Linear xanthomas (approximately 0.5–1.0 cm in size) with firm consistency were observed bilaterally on the ankles (The blue arrow indicates the site of the lesion). (**B**) The Sanger sequencing results showed that the proband had a homozygous *ABCG5* c.1166G>A (p.Arg389His) variant, which was inherited from both her father and mother (red arrows indicate mutation sites).

https://doi.org/10.2147/CCID.S555492

affect lipoprotein stability and promote atherosclerotic plaque formation.[3,8,10] Accumulation of excess plant sterols occurs in the skin and blood vessels.[11] Elevated free sterols also accumulate in platelet membranes, potentially dysregulating platelet activation pathways,[12] leading to macrothrombocytopenia and bleeding tendencies.[13] Our patient did not exhibit hemoglobin or platelet abnormalities, presenting primarily with xanthomas and hypercholesterolemia, underscoring the importance of early diagnosis.

Literature review indicates that sitosterolemia presenting with xanthomas in children is often misdiagnosed as homozygous FH (HoFH).[14] As noted by the American Heart Association in 2015, patients with HoFH typically develop xanthomas before age 10, whereas those with heterozygous FH (HeFH) usually present in adulthood.[15] In HoFH due to autosomal dominant mutations (eg, in LDLR, PCSK9, APOB), parents are typically heterozygotes with elevated LDL-C levels and a family history of premature ASCVD. In contrast, for autosomal recessive hypercholesterolemia (due to LDLRAP1 mutations), parental LDL-C levels may be normal.[16] Sitosterolemia is an autosomal recessive disorder involving *ABCG5/ABCG8* mutations and increased plant sterol absorption. Its clinical features overlap with HoFH,[13] as both can present with elevated LDL-C and total cholesterol levels, as well as early-onset xanthomas at multiple sites, making clinical differentiation crucial. In individuals with *ABCG5/ABCG8* mutations, plasma plant sterol levels are markedly elevated (30–200 times normal),[1,17] and excess plant sterols accumulate in the skin and vasculature. Definitive diagnosis relies on genetic testing (*ABCG5/ABCG8*) or serum plant sterol profile analysis. Significant differences exist in the treatment and prognosis of these two conditions, stemming from their distinct pathogenic mechanisms. Cholesterol elevation in sitosterolemia is more dependent on dietary sterol intake. Consequently, LDL-C levels in sitosterolemia patients may decrease significantly with appropriate dietary modifications, unlike in FH.

Diagnosis is often delayed in the majority of patients with sitosterolemia. A case series reported an average diagnostic delay of 28.8 years from symptom onset to diagnosis,[18] partly because many dermatologists and non-specialists are unfamiliar with its manifestations. At the patient's initial visit, presenting only with xanthomas, the diagnosis was challenging, as the clinicians had not previously encountered such a case. Subsequent literature review during follow-up revealed that both FH and sitosterolemia can present with xanthomas, and early diagnosis and intervention are crucial in young children. Due to the unavailability of plant sterol testing locally, the diagnosis was ultimately confirmed through lipid profiling and genetic testing. Unfortunately, the child died before treatment could be implemented. Reasons for underdiagnosis and misdiagnosis of sitosterolemia include: 1) Low clinical suspicion for rare diseases among physicians, particularly dermatologists and non-specialists. 2) Limitations in testing: routine lipid panels cannot distinguish plant sterols from cholesterol. Quantifying plasma plant sterols typically requires specialized techniques like gas-liquid chromatography (GLC), gas chromatography/mass spectrometry (GC/MS), or high-performance liquid chromatography (HPLC),[19] which are not widely available in clinical laboratories, especially in underdeveloped regions. Genetic testing for sitosterolemia is also not routinely accessible in many areas. 3) Overlapping clinical features with FH, particularly regarding xanthomas. For patients with refractory FH showing insufficient LDL-C response to statins, re-evaluation for sitosterolemia, including genetic testing, should be considered to avoid missed diagnosis.

Treatment for sitosterolemia includes dietary and pharmacological management. Plant sterols (eg, sitosterol, campesterol, stigmasterol) are sterol molecules naturally present in plant-based oils, fruits, vegetables, nuts, and grains.[20] Dietary restriction of plant sterols forms the foundation of therapy,[21] although this can be challenging, especially for infants. Patients with sitosterolemia often respond poorly to statins alone, because HMG-CoA reductase activity is already maximally inhibited. However, statins are effective in reducing LDL cholesterol, at least in some sitosterolemic patients.[8] While medications including ezetimibe and bile acid sequestrants like cholestyramine are established standard treatments, consensus on managing sitosterolemia, particularly in children under 2 years, is lacking. Ezetimibe, a sterol absorption inhibitor targeting the NPC1L1 transporter, has become a first-line therapy for patients with sitosterolemia.[22]

Genetic counseling is essential. Sitosterolemia is autosomal recessive. In this case, both parents are carriers, conferring a 25% risk for affected offspring in each pregnancy. The parents were advised to seek reproductive genetic counseling for future pregnancies. Other relatives of the parents are also at risk of being carriers. Once the causative mutation is identified in an affected family member, carrier testing for at-risk relatives and prenatal testing for high-risk pregnancies become possible options.[23]

Conclusion

Sitosterolemia is a rare multisystem disorder. Despite its rarity, its treatable nature and the significant harms of misdiagnosis warrant high clinical vigilance. This case report describes a patient presenting solely with cutaneous xanthomas, ultimately diagnosed with sitosterolemia due to a homozygous *ABCG5* c.1166G>A (p.Arg389His) mutation. This case emphasizes that sitosterolemia should be suspected in infants presenting with cutaneous xanthomas and elevated cholesterol levels, or in patients with early-onset xanthomas and hypercholesterolemia who respond poorly to statin therapy. Genetic testing (*ABCG5/ABCG8*) and serum plant sterol analysis are the diagnostic gold standards. Early diagnosis and treatment can significantly reverse the disease course.

Ethical Approval

We thank the institution of Chengdu Pidu District Hospital of Traditional Chinese Medicine for granting us approval to publish this information. Institutional approval was required to publish the case details.

Informed Consent

Written informed consent was obtained from the patient's legal guardian for the publication of the clinical details and medical images.

Acknowledgments

We thank the patient's legal guardian for authorizing the use of the clinical information and for supporting medical research. All case details described in this manuscript have been published with the written informed consent of the patient's legal guardian.

Disclosure

The authors declare no conflicts of interest.

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