



Case Report

Early tendon xanthomas in a breastfed toddler with sitosterolemia misdiagnosed as familial hypercholesterolemia: Successful treatment with ezetimibe

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ABSTRACT

Sitosterolemia is a rare autosomal recessive disorder of sterol metabolism, often misdiagnosed as familial hypercholesterolemia due to overlapping features of tendon xanthomas and severe hypercholesterolemia. We report a 1.5-year-old breastfed female who presented with multiple tendon xanthomas, marked low-density lipoprotein-cholesterol elevation, and poor response to statins, dietary measures, and cholestyramine. Genetic analysis confirmed a compound heterozygous mutation in *ABCG8*. Following initiation of ezetimibe, her lipid profile normalized, and xanthomas stabilized without adverse effects. This case underscores the need to consider sitosterolemia in early-onset xanthomas while highlighting the exacerbating effect of breastfeeding and supporting the safe use of ezetimibe in young children.

Keywords: *ABCG8*, Cholestyramine, Ezetimibe, Familial hypercholesterolemia, Sitosterolemia

INTRODUCTION

Sitosterolemia (also known as phytosterolemia) is a rare autosomal recessive lipid metabolism disorder characterized by increased intestinal absorption and decreased biliary excretion of plant sterols due to mutations in genes encoding ATP-binding cassette, subfamily G5 (*ABCG5*) or G8 (*ABCG8*).^[1] It leads to the buildup of plant sterols, including sitosterol, stigmasterol, and campesterol, along with cholesterol, resulting in tendon, tuberous, and intertriginous xanthomas, hemolytic anemia, thrombocytopenia, arthritis, splenomegaly, and premature atherosclerosis.^[2] Although its true prevalence is uncertain, it has historically been considered rare and underdiagnosed.^[2] Due to similar biochemical and phenotypic features, sitosterolemia is often misdiagnosed as familial hypercholesterolemia (FH). Although sitosterolemia is traditionally considered a differential diagnosis for non-lipemic xanthomas, patients with sitosterolemia also hyperabsorb cholesterol and have elevated serum low-density lipoprotein-cholesterol (LDL-C), thereby mimicking FH.^[3] However, in contrast to FH, hypercholesterolemia in patients with sitosterolemia is remarkably responsive to a low-cholesterol diet and/or bile acid sequestrants.^[4] Importantly, in unresponsive or poorly compliant cases, the drug ezetimibe, which blocks the Niemann–Pick C1-Like 1 (NPC1L1) transporter, stops the intestines from

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absorbing plant sterols and cholesterol, leading to significant biochemical and clinical improvements in affected individuals.^[5] While ezetimibe is commonly used in adults, there is limited experience in children, especially in those under 10 years of age.^[6,7] Infants and toddlers present a special challenge due to their high sterol absorption, due to breastfeeding, which naturally contains a higher concentration of sterols per body weight, more than formula feeds or adult diet.^[8] This article discusses a breastfed toddler girl with sitosterolemia who was initially misdiagnosed with FH and ultimately successfully treated with ezetimibe.

CASE DESCRIPTION

A 1.5-year-old female, born to 3rd degree consanguineous parents, was brought in with multiple yellowish nodules over the extensor surfaces of limbs, first noticed at 4 months of age. These had gradually increased in size and distribution, involving the elbows, wrists, thighs, and ankles. The swellings were firm, shiny, yellow, waxy, and non-tender, consistent with tendon xanthomas. Family history was significant for hypercholesterolemia in her father, who had been on statin therapy for the past 5 years. She was started elsewhere on tablets of atorvastatin 5 mg once daily at 1 year of age without any clinical improvement. The child was still on almost exclusive breastfeeding due to poor weaning practices at home.

At presentation, anthropometry revealed a weight of 8.2 kg (−2.32 standard deviation score [SDS]), length of 74 cm (−2.66 SDS), and a head circumference of 46 cm (−1.16 SDS). Systemic examination revealed multiple tendon xanthomas over the elbows and ankles [Figure 1a-d], with no hepatosplenomegaly or cardiac murmurs. Complete blood counts, liver, and renal function tests were normal. Fasting lipid profile revealed total cholesterol of 556 mg/dL ($n < 170$ mg/dL), LDL-C of 453 mg/dL ($n < 110$ mg/dL), and normal high-density lipoprotein (HDL) and triglyceride levels. Ultrasound abdomen, ophthalmological examination, and 2D-echocardiography ruled out any hyperlipidemia-associated changes.

Lack of biochemical and clinical response to statins for 6 months suggested an alternative etiology, masquerading as FH. The parents were counseled to wean the child off breastfeeds, cholestyramine was added at 240 mg/kg/day, and dietary measures, including restriction of sterol-rich foods (peanuts, soybeans, chocolate, and eggs), were initiated. However, biochemical control was poor in view of poor adherence due to the small age of the child and the inability to wean off breastfeeds completely. Cholestyramine, too, was poorly tolerated because of gastrointestinal side effects. By this time, whole-exome sequencing (WES) confirmed compound heterozygous variants in *ABCG8*: a nonsense mutation in exon 4 (c.361C>T, p.Arg121Ter,

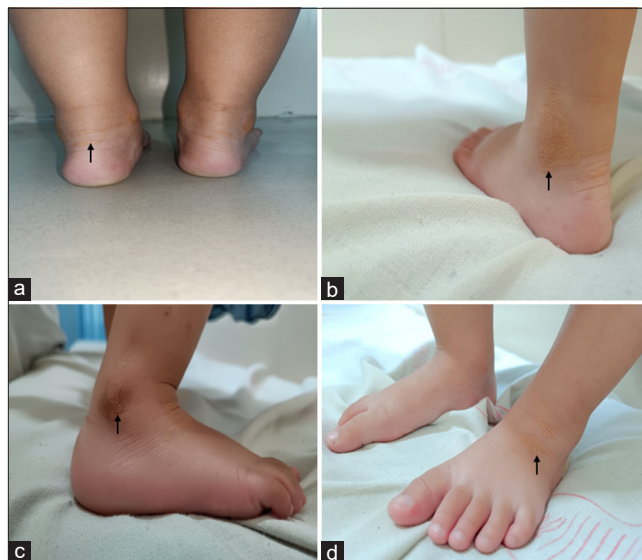


Figure 1: A 1.5-year-old female child who presented with (a) multiple tendon xanthomas (solid arrows) over posterior ankle creases, (b) lateral malleolus of the left lower limb (solid arrows), (c) lateral malleolus of the right lower limb (solid arrows), (d) anterior surface of ankle joint (solid arrows).

likely pathogenic) and a start-loss variant in exon 1 (c.2T>C, p.Met1Thr, VUS), consistent with sitosterolemia. The carrier status of parents could not be checked owing to financial constraints. She was started on ezetimibe at 10 mg/day, the lowest pediatric dose. Over the next 6 months, her lipid profile normalized, and xanthomas reduced in number without the appearance of any new lesions. No side effects were noted, and treatment was well tolerated.

DISCUSSION

Sitosterolemia (OMIM #210250 and #618666) is an inherited disorder caused by mutations in the *ABCG5/ABCG8* genes, which form heterodimeric transporters that actively excrete sterols into bile and limit absorption at the intestinal epithelium. Failure of this active transport mechanism leads to excessive absorption and reduced excretion of plant sterols into and from the body, respectively. Skin symptoms include tendon and tuberous xanthomas, which often appear in early infancy due to hypercholesterolemia. Hematological manifestations include hemolytic anemia, macrothrombocytopenia, and hepatosplenomegaly in severe cases.^[2] Cardiovascular problems, such as early coronary artery disease and aortic valve stenosis, may develop during adolescence or early adulthood and are the main cause of sudden death in these patients.^[7] Hypercholesterolemia and xanthoma are two of the most common manifestations in patients with sitosterolemia, present in about 85% of cases.^[7] Our case had both, without hematological or cardiovascular abnormalities.

The overlap with FH, especially concerning high cholesterol and LDL-C levels, and tendon xanthomas, particularly in a background of a breastfeeding child, often leads to misdiagnosis. It is thought that stigmaterol, which accumulates in sitosterolemia, inhibits the processing of the transcription factor sterol regulatory element binding protein-2, which is involved in transcription of the hepatic LDL receptor (LDLR). Accordingly, hepatic LDLR transcription is assumed to be inhibited, thereby increasing circulating cholesterol.^[9] Breastmilk also contains around 100 mg/dL of sitosterol, making consumption at around 500 mg/day in an infant ingesting 500 mL of breastmilk, greater than in an adult in terms of proportion with body weight. The accumulation of non-cholesterol sterols contributes to the very low cholesterol biosynthesis in cases of sitosterolemia by maximally inhibiting hydroxymethylglutaryl-CoA reductase, leading to the speculation that the severe hypercholesterolemia observed in infantile sitosterolemia during breastfeeding reflects reduced LDL catabolism rather than increased cholesterol biosynthesis. Tada *et al.* also reported that weaning was associated with lower cholesterol and better metabolic control in Japanese infants.^[8] This is also the reason why statins, which tend to inhibit cholesterol synthesis, do not work in sitosterolemia.^[10]

However, unlike FH, sitosterolemia responds well to dietary restrictions on sterols and to medications that block intestinal sterol absorption.^[2] Normally, patients with sitosterolemia absorb 15–60% of ingested sitosterol, compared with 5% in normal individuals, leading to very high levels of plant sterols in the blood, as measured by gas chromatography–mass spectrometry analysis.^[3] Limiting foods high in sterols—such as peanuts, soybeans, rapeseed oil, sesame oil, rice oil, margarine, avocado, chocolate, animal liver, eggs, and shellfish—is crucial, but it often is not enough or feasible on its own, especially for small children, as seen in our case. Bile acid sequestrants, such as cholestyramine, are

not well tolerated in young children due to diarrhea and fat malabsorption, leading to poor adherence. Ezetimibe, which blocks NPC1L1 and reduces sterol absorption, is now the most effective treatment, especially in children.^[2] Compared to the global pediatric literature, our case adds to the limited data on the use of various modalities in very young children with sitosterolemia. Niu *et al.* described administering ezetimibe to an infant at 3 months, though a response was noted only after reintroduction at 2 years.^[6] Tada *et al.* reported that infants as young as 10–18 months showed significant improvement after weaning.^[8] Park *et al.* detailed the case of a 15-month-old Korean girl who was misdiagnosed with FH; she saw her cholesterol levels normalize with dietary changes and cholestyramine before ezetimibe was introduced.^[3] Ba *et al.* (2021) documented an 8-year-old boy with coronary atherosclerosis who improved with ezetimibe and dietary therapy.^[7] Miroshnikova *et al.* reported three pediatric cases aged 1–6 years who showed consistent biochemical improvement with dietary restriction alone on a low-cholesterol diet, with one requiring plasmapheresis.^[9] Thus, our case is notable as one of the youngest toddlers successfully treated with ezetimibe after initial treatment failure, supporting its safety and effectiveness in this age group. Table 1 summarizes the treatments and responses of various reported pediatric cases of sitosterolemia in the literature.

Our case is unique for several reasons. First, the child showed tendon xanthomas as early as 4 months, which is unusual and indicates the severe nature of the disorder. Second, she was breastfed until 15 months, which explains the poor biochemical response during initial treatment in our patient. Third, after dietary restrictions and a poor response to cholestyramine, our patient showed a remarkable improvement with ezetimibe, suggesting that it should be considered early in pediatric sitosterolemia, even in very young children.

Table 1: Summary of the treatment and response of various reported pediatric cases of sitosterolemia.

Author and Year (Reference)	Age at diagnosis and presentation	Mutation	Therapy	Outcome
Niu <i>et al.</i> , 2010 ^[6]	5 cases, lowest age 3 months, hyperlipidemia	<i>ABCG5</i> mutations	Ezetimibe	No response in infancy; effective after 2 years
Tada <i>et al.</i> , 2015 ^[8]	4 cases, 10–18 months, hyperlipidemia	<i>ABCG5</i> mutations	Weaning+ezetimibe	Dramatic cholesterol/sterol reduction; xanthoma regression
Park <i>et al.</i> , 2014 ^[3]	15 months, hyperlipidemia	<i>ABCG5</i> compound heterozygous	Diet+cholestyramine, later ezetimibe at 64 months	Normalization and later relapse
Ba <i>et al.</i> , 2021 ^[7]	8 years, premature atherosclerosis	<i>ABCG5</i> intron mutations	Ezetimibe+diet	Lipid-lowering, improved clinical status
Miroshnikova <i>et al.</i> , 2023 ^[9]	1–6 years, hyperlipidemia	<i>ABCG8</i> variants	Diet alone	Marked cholesterol and sterol reduction with dietary restriction

CONCLUSION

Sitosterolemia should be suspected in infants and children presenting with severe hypercholesterolemia and xanthomas, especially when the response to statins is poor. Our report highlights three important points: the diagnostic challenge of distinguishing sitosterolemia from FH, the adverse impact of breastfeeding on sterol levels, and the dramatic efficacy of ezetimibe in toddlers. Early diagnosis and timely initiation of ezetimibe can prevent complications, stabilize lesions, and improve long-term outcomes in pediatric sitosterolemia.

Ethical approval: Institutional Review Board approval is not required.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms from the patient's parents/guardians. In the form, they have given their consent for the patient's images and other clinical information to be reported in the journal. They understand that the names and initials will not be published and due efforts will be made to conceal the patient's identity, but anonymity cannot be guaranteed.

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REFERENCES

1. Berge KE, Tian H, Graf GA, Yu L, Grishin NV, Schultz J, *et al.* Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. *Science* 2000;290:1771-5.
2. Tada H, Nomura A, Ogura M, Ikewaki K, Ishigaki Y,

- Inagaki K, *et al.* Diagnosis and management of sitosterolemia 2021. *J Atheroscler Thromb* 2021;28:791-801.
3. Park JH, Chung IH, Kim DH, Choi MH, Garg A, Yoo EG. Sitosterolemia presenting with severe hypercholesterolemia and intertriginous xanthomas in a breastfed infant: Case report and brief review. *J Clin Endocrinol Metab* 2014;99:1512-8.
4. Kidambi S, Patel SB. Sitosterolaemia: Pathophysiology, clinical presentation and laboratory diagnosis. *J Clin Pathol* 2008;61:588-94.
5. Sudhop T, Lütjohann D, Kodal A, Igel M, Tribble DL, Shah S, *et al.* Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002;106:1943-8.
6. Niu DM, Chong KW, Hsu JH, Wu TJ, Yu HC, Huang CH, *et al.* Clinical observations, molecular genetic analysis, and treatment of sitosterolemia in infants and children. *J Inherit Metab Dis* 2010;33:437-43.
7. Ba H, Peng H, He X, Cheng L, Lin Y, Li X, *et al.* Sitosterolemia with atherosclerosis in a child: A case report. *Front Pediatr* 2021;9:668316.
8. Tada H, Kawashiri MA, Takata M, Matsunami K, Imamura A, Matsuyama M, *et al.* Infantile cases of sitosterolaemia with novel mutations in the ABCG5 gene: Extreme hypercholesterolaemia is exacerbated by breastfeeding. *JIMD Rep* 2015;21:115-22.
9. Miroshnikova VV, Gusarova VA, Utkina EA. Pediatric patients with sitosterolemia: Clinical features and responsiveness to therapy. *J Pers Med* 2023;13:1054.
10. Yoo EG. Sitosterolemia: A review and update of pathophysiology, clinical spectrum, diagnosis, and management. *Ann Pediatr Endocrinol Metab* 2016;21:7-14.

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