

## Case Report

# A case of sitosterolemia due to compound heterozygous mutations in *ABCG5*: clinical features and treatment outcomes obtained with colestimide and ezetimibe

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**Abstract.** Sitosterolemia is a rare, autosomal recessively inherited disorder of lipid metabolism caused by mutations in the “ATP-binding cassette, subfamily G” member 5 and 8 proteins (encoded by the *ABCG5* and *ABCG8* genes, respectively), which play critical roles in the intestinal and biliary excretion of plant sterols. We report the clinical features and treatment outcomes of an 18-month-old Japanese girl with sitosterolemia, who presented with multiple linear and intertriginous xanthomas around the joint areas. Serum lipid analyses revealed elevated levels of total cholesterol (T-Chol: 866 mg/dL), low density lipoprotein-cholesterol (LDL-C: 679 mg/dL), and plant sterols (sitosterol: 24.6 mg/dL, campesterol: 19.2 mg/dL, stigmasterol: 1.8 mg/dL). Compound heterozygous mutations (p.R419H and p.R389H) were identified in *ABCG5*. The patient was placed on a low cholesterol/low plant sterol diet and treated with colestimide (a bile acid sequestrant) and ezetimibe (an NPC1L1 inhibitor). Serum T-Chol and LDL-C levels decreased to normal within 2 mo, and plant sterol levels decreased by 30% within 4 mo. The xanthomas regressed gradually, and almost completely disappeared after 1.5 yr of treatment. No further reductions of plant sterol levels were observed. Long-term follow-up is important to verify appropriate therapeutic goals to prevent premature atherosclerosis and coronary artery disease.

**Key words:** sitosterolemia, xanthomas, *ABCG5*, colestimide, ezetimibe

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## Introduction

Sitosterolemia (Online Mendelian Inheritance in Man [OMIM database, at <https://www.omim.org/>] catalog entry #210250) is a rare disorder of lipid metabolism, caused by autosomal recessive inheritance, that is characterized by extreme elevation of serum plant sterols (1). It is caused by mutations in either of two genes, *ABCG5* and *ABCG8*, which encode the “ATP-binding cassette, subfamily G” member 5 and

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Received: September 6, 2016

Accepted: November 22, 2016

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8 proteins (*ABCG5* and *ABCG8*), respectively. These proteins localize to the apical membranes of enterocytes and hepatocytes, and play critical roles in the intestinal and biliary excretion of plant sterols (2, 3). The main clinical features of sitosterolemia are xanthomas and premature atherosclerosis. Arthralgia, hemolytic anemia, macrothrombocytopenia, and splenomegaly are occasionally present (4). Although sitosterolemia was originally reported in patients with xanthomas, despite the patients' normal serum total cholesterol (T-Chol) levels (5), most pediatric patients of sitosterolemia have exhibited elevated levels of T-Chol and low density lipoprotein-cholesterol (LDL-C) (6–8). Thus, sitosterolemia shares primary clinical features with familial hypercholesterolemia (FH) and is possibly misdiagnosed as homozygous FH (7, 9). We have observed a case of sitosterolemia manifesting progressive linear and intertriginous xanthomas around the joint areas, and we recently reported the histopathological characteristics of these sitosterolemic xanthomas from a dermatological perspective (10). Here, we report the detailed clinical features and treatment outcomes of this case of sitosterolemia.

### Case Report

An 18-mo-old Japanese girl was referred to our department for the evaluation of multiple xanthomas. She was born from healthy, non-consanguineous parents, without any adverse events in the perinatal period. There was no family history of dyslipidemia, xanthomas, premature cardiovascular disease, or sudden death. Her mother first noticed the presence of faint yellowish streaks on the patient's ankles and wrists during the neonatal period, and lesions gradually became obvious at 6 mo of age (Fig. 1A). She was exclusively breastfed until 5-mo-old, was introduced to a weaning diet at around 6 mo of age, and preferred to eat chocolate as a snack after reaching the age of 1 yr.

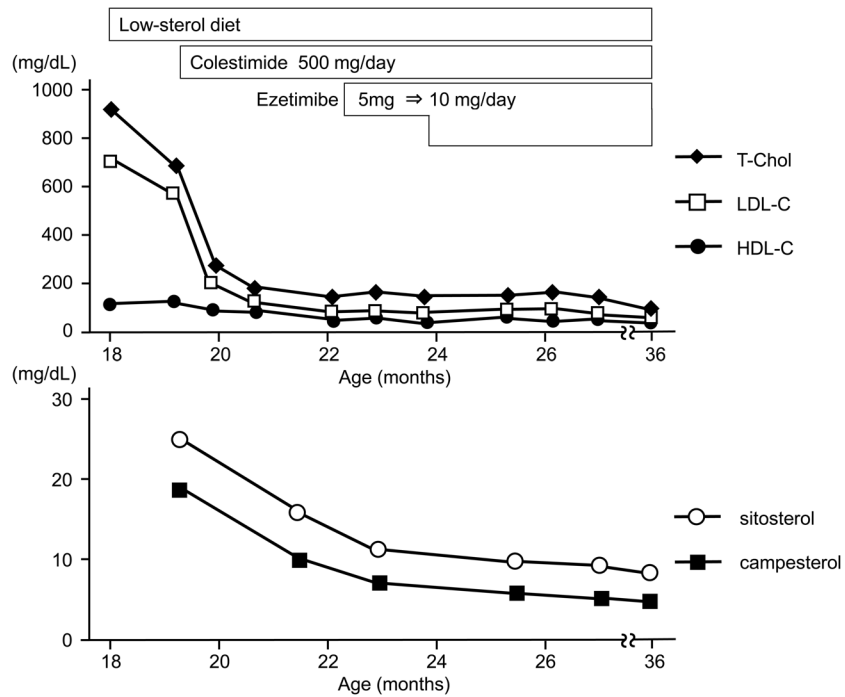
The patient's height was 77.0 cm (−0.9

SD), and weight was 9.2 kg (−0.7 SD). Physical examination revealed multiple yellowish, linear and intertriginous xanthomas on her wrists, elbows, ankles, and knees (Figs. 1B and C). Neither bulky xanthomas on her eyelids, nor corneal arcus, were observed. No other physical abnormalities suggesting secondary hypercholesterolemia, such as hypothyroidism or nephrotic syndrome, were observed. Laboratory examinations (Table 1) revealed marked elevations in serum T-Chol (866 mg/dL) and serum LDL-C (679 mg/dL). High-density lipoprotein-cholesterol (HDL-C) and triglyceride (TG) levels were normal, and the level of lipoprotein Apo B was elevated (251 mg/dL). No other abnormal findings were observed in other tests (including urinalysis, peripheral blood count, and thyroid function tests). Both parents showed almost normal serum lipid profiles at fasting; and the LDL receptor activity levels of lymphocytes was 98% in the patient's father, and 60% in the patient's mother (Table 2). These findings excluded the diagnosis of homozygous FH, and suggested the diagnosis of either sitosterolemia or autosomal recessive hypercholesterolemia. Serum plant sterol concentrations were then measured using high performance liquid chromatography, and were found to be elevated about 100-fold above normal levels (sitosterol: 24.6 mg/dL, campesterol: 19.2 mg/dL, stigmasterol: 1.8 mg/dL). Mild increases in serum plant sterol concentrations were observed in both parents, suggesting heterozygosity of sitosterolemia (Table 2). The diagnosis of sitosterolemia was confirmed by the identification of known, compound heterozygous mutations (p.R419H and p.R389H) in the *ABCG5* gene, and both parents were found to be heterozygous carriers for each mutation (3). No mutations were found in the *ABCG8* gene.

After establishing the diagnosis of sitosterolemia, a low cholesterol/low plant sterol diet and the administration of colestimide (250 mg, twice daily), a bile acid sequestrant, were prescribed. Within 2 mo, the patient's serum



**Fig. 1.** Faint xanthomas noticed by patient’s mother on patient’s wrists at 6 mo of age (arrow) (A). Pronounced xanthomas were observed at 18 mo of age on the wrists and elbows (B), ankles and knees (C).



**Fig. 2.** Time-course of plasma cholesterol and plant sterol levels. Treatments are indicated at the top of the graph. Closed diamond indicates T-Chol, open square indicates LDL-C, closed circle indicates HDL-C, open circle indicates sitosterol, and closed square indicates campesterol.

T-Chol and LDL-C levels decreased dramatically and to normal levels: 167 mg/dL and 110 mg/dL, respectively (Fig. 2). The patient's plant sterol levels also decreased by 50%; however, they remained elevated at about 50-fold above normal levels (sitosterol: 14.2 mg/dL, campesterol: 10 mg/dL, stigmasterol: 0.64 mg/dL). Therefore, co-administration of ezetimibe (10 mg, once daily), an inhibitor of the Niemann-Pick C1-like 1 (NPC1L1) protein, was started. After 4 mo of ezetimibe treatment, plant sterol levels decreased further by approximately 30% (sitosterol: 6.8 mg/dL, campesterol: 4.3 mg/dL). No further reductions in plant sterol levels were observed, and they remained elevated at higher levels than normal. Pharmacotherapy with colestimide and ezetimibe was well tolerated; no serious treatment-related adverse events, such as rhabdomyolysis, were observed. The xanthomas regressed gradually, and disappeared almost completely after 1 yr of treatment (Fig. 3). During treatment, the patient's physical growth (height and weight) was within one standard deviation ( $-1.0$  SD) of that of normal Japanese girls. At 3 yr of age, her height was 88.7 cm ( $-1.0$  SD) and her weight was 11.1 kg ( $-1.25$  SD). Ultrasonography of her internal carotid arteries showed no irregularities, and no abnormal changes that would reflect cardiac ischemia were detected by electrocardiogram.

### Discussion

We have identified a Japanese girl with sitosterolemia who presented with multiple xanthomas and extreme hypercholesterolemia (10). Xanthoma is rarely observed in pediatric patients; accurate diagnoses are critically important for planning appropriate treatments and making accurate prognoses. Homozygous FH due to an LDL-receptor defect is most often suspected when both parents present hypercholesterolemia (9). In this case, although the patient's mother presented slightly elevated T-Chol levels, the patient's father's T-Chol levels

**Table 1** Results of the laboratory examinations of the patient at 18 mo of age

WBC	6,220 / $\mu$ L
RBC	$408 \times 10^4$ / $\mu$ L
Hb	10.6 g/dL
Ht	32.3 %
Plt	$36.9 \times 10^4$ / $\mu$ L
TP	6.7 g/dL
ALB	4.5 g/dL
T-Bil	0.3 mg/dL
ALT	12 U/L
AST	28 U/L
$\gamma$ -GTP	7 U/L
LDH	219 U/L
Cr	0.15 mg/dL
BUN	15 mg/dL
T-Chol	866 mg/dL
LDL-C	679 mg/dL
HDL-C	46 mg/dL
TG	107 mg/dL
ApoA-I	98 mg/dL
ApoA-II	17.7 mg/dL
ApoB	251 mg/dL
ApoC-II	5.3 mg/dL
ApoC-III	6.8 mg/dL
ApoE	9.7 mg/dL
TSH	0.93 $\mu$ U/mL
FT4	1.08 ng/dL

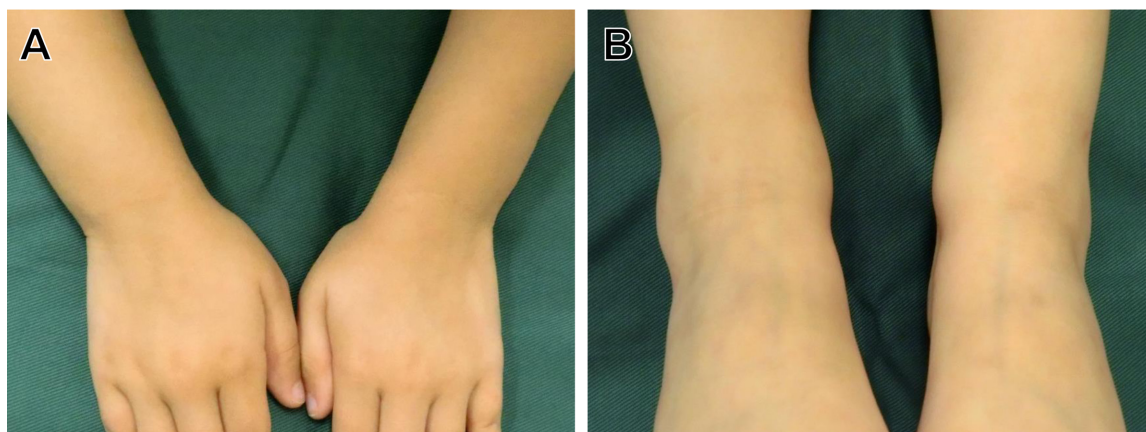
were normal and his LDL-receptor activity levels were also normal. Commercially available tests for serum plant sterol levels led us to the diagnosis of sitosterolemia.

Sitosterolemia is caused by homozygous or compound heterozygous mutations in either the *ABCG5* or *ABCG8* genes (2, 3). The *ABCG5* and *ABCG8* proteins form heterodimers and act as preferential efflux pumps of plant sterols from enterocytes and hepatocytes into the lumen (8, 9). Most Asian sitosterolemia patients (including our case) have mutations in *ABCG5*, whereas most Caucasian patients have *ABCG8* mutations (8, 11). Plant sterols such as sitosterol, campesterol, and stigmasterol are structurally similar to cholesterol; however, they are rarely detected in healthy subjects. Sitosterolemic patients typically exhibit serum concentrations of plant sterols that are 30- to 100-fold greater than normal levels (8,

**Table 2** Serum lipid concentrations and LDL-receptor activity values in the patient and in her parents

	Patient	Mother	Father	Reference value
T-Chol (mg/dL)	866	211	118	150–219
LDL-Chol (mg/dL)	679	139	62	70–139
HDL-Chol (mg/dL)	46	57	43	40–80
TG (mg/dL)	107	58	45	50–149
LDL-receptor activity (%)	50	60	98	≥ 80
Sitosterol (mg/dL)	24.6	1	0.5	0.24 ± 0.07
Campesterol (mg/dL)	19.2	2	0.9	0.49 ± 0.14
Stigmasterol (mg/dL)	1.8	nd	nd	0.26 ± 0.06

nd: not determined.



**Fig. 3.** At 3 yr of age, xanthomas disappeared almost completely from the patient's wrists (A) and ankles (B).

11). Importantly, most pediatric patients with sitosterolemia not only show elevated serum plant sterol levels, but also have significantly elevated serum cholesterol levels, which can be up to 1,000 mg/dL (6–8). Although the mechanism for hypercholesterolemia in young patients is not clearly understood, hyperabsorption of cholesterol and suppression of LDL-receptor activity have been suggested (11, 12). It is noteworthy that our patient displayed xanthomas as early as during the neonatal period, and that these progressed despite the patient being exclusively breastfed (breast milk contains only very small amount of plant sterols). Because the LDL-receptor activity levels of both mother and patient were approximately half the value of normal levels,

our patient's very early onset of xanthomas might be due to the presence of heterozygous FH, in addition to sitosterolemia (6, 7).

In contrast to patients with other forms of hypercholesterolemia (such as FH), patients with sitosterolemia usually respond very well to a low cholesterol diet and/or to bile acid sequestrants such as colestimide and colestyramine (8, 11). However, for most patients, dietary restriction of plant sterols is very difficult to adhere to (1, 6–8); furthermore, especially in pediatric patients, growth retardation due to strict diet therapy should also be considered (1, 13). Paradoxically, in other forms of hypercholesterolemia, a plant sterol-rich diet is usually recognized as being protective against coronary heart disease (14). Because the

transporter protein NPC1L1 has a significant role in the intestinal absorption of cholesterol and plant sterols, ezetimibe (an NPC1L1 inhibitor) effectively inhibits the intestinal absorption of both cholesterol and plant sterols in sitosterolemia (15–17), and several reports have shown the effectiveness of ezetimibe in pediatric sitosterolemia (6, 7). By contrast, statins (which are hydroxymethylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) are usually not effective in sitosterolemic patients (18). Although ezetimibe has been officially approved as a treatment for adult sitosterolemia, neither ezetimibe nor colestimide have yet been established as safe for treating childhood sitosterolemia. Therefore, according to ethical guidelines, we informed the patient's parents of the expected medical risks and benefits of each drug, and we obtained their written, informed consent before starting the treatment. In our patient, treatment with colestimide and the low cholesterol diet effectively normalized serum T-Chol levels, and ezetimibe was effective in further decreasing serum levels of plant sterol. This clinical course is compatible with previously reported pediatric cases that were treated with either the same regimen or with ezetimibe alone (6, 7).

Whether the normalization of both total cholesterol and plant sterol is essential, or if only the normalization of total cholesterol is sufficient, has not yet been clearly evaluated. In mouse models of sitosterolemia (ABCG5-deficient, ABCG8-deficient, or double ABCG5- and ABCG8-deficient mice), accumulation of plant sterol alone induced complex cardiac lesions (19). Several studies have indicated that even mild elevations of plant sterol levels may increase the risk of cardiovascular disease (20). Early onset myocardial infarction due to premature atherosclerosis has been reported in a 5-yr-old patient of sitosterolemia (21). Our patient might still be at risk for cardiovascular disease; therefore, long-term and cautious follow-up of this patient is important to maintain appropriate therapeutic goals for reducing serum

plant sterol levels, thus preventing premature atherosclerosis and coronary artery disease (22).

### Acknowledgements

We thank Ms. Yuko Kanatani for her excellent technical assistance.

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